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NATURE OF VEGETATIONS OF BACTERIAL ENDOCARDITIS

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The history of the investigations of endocardial vegetations has been reviewed by Perry [1] in his monograph and by Gross in his series of papers on rheumatic endocarditis. It suffices to mention here that in the early part of the nineteenth century, Corvisart [2] thought that the vegetations of bacterial endocarditis represented syphilis, because of their resemblance to venereal warts. This was followed by the belief that they were made of "coagulable lymph" (e. g., Cayley [3]). However, it soon became apparent that the lesions resembled thrombi inasmuch as they were thought to be composed of platelets, fibrin and blood cells.

The latter time-honored concept has become deeply rooted in text-books and in current literature. It is now generally assumed without question that the bulk of each of these characteristic shaggy vegetations is simply a thrombotic mass of platelets with enmeshed fibrin, red blood cells and leukocytes, often capped by clumps of bacteria. This thrombus is thought to be deposited from the blood flowing over the inflamed endocardial surface of the valve (MacCallum [4]; Boyd [5]). It is agreed that frequently areas of necrosis may be seen within the thrombi and that subsequently organization and calcification may take place.

For purposes of orientation in this discussion, it may be stated that a typical vegetation of acute or subacute bacterial endocarditis is com-

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1. Perry, C. B.: Bacterial Endocarditis, Bristol, John Wright & Sons, Ltd., 1935.

2. Corvisart, J. N.: A Treatise on the Diseases and Organic Lesions of the Heart and Great Vessels, translated by C. H. Hebb, London, Underwood & Blacks, 1813.

3. Cayley, W.: M. Times & Gaz. **2**:509, 1877.

4. MacCallum, W. G.: A Text-Book of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1937, pp. 240-245.

5. Boyd, W.: A Text-Book of Pathology, ed. 1, Philadelphia, Lea & Febiger, 1932, p. 148.

monly regarded as being composed of three rather poorly defined zones (MacCallum [4]; Hadfield and Garrod [6]):

Zone 1. A proximal layer of fibrin, platelets, red blood cells and leukocytes with more or less necrosis.

Zone 2. A layer of bacteria.

Zone 3. An outermost layer of fibrin in which red blood cells and a sprinkling of leukocytes are enmeshed.

CURRENT VIEW

The existence in general of these zones is not denied. Differences arise, however, in the interpretation of the zone underlying the bacteria. This, zone 1, exclusive of the bacterial layer, usually makes up the bulk of the vegetation, so that an accurate knowledge of its composition is the sine qua non of a true concept of the histogenesis of the lesion. Those who assume a thrombotic origin consider this zone to be composed of platelets, fibrin and blood cells which have been deposited from the blood stream within the cardiac chambers and which have subsequently undergone more or less necrosis.

OPPOSING VIEW

However, papers have appeared from time to time in the German literature suggesting that these lesions are nonthrombotic (Baldasarri [7]). More recently, Jaffé [8] reemphasized the view that the vegetations are not thrombi deposited on the valve but are derived from the tissue of the valve itself. Nevertheless, the thrombotic concept persists. One is unable to find in the literature actual studies of bacterial vegetations which show irrefutably that they are or are not of valvular origin. Vegetations have, of course, been previously sectioned and carefully studied, but studies of *differentially stained* sections with this issue in mind appear wanting except in rare instances.

MATERIALS AND METHODS

Vegetations from 5 hearts with acute and 19 with subacute bacterial endocarditis were sectioned and stained with hematoxylin-eosin, Weigert's elastica Van Gieson, Mallory's phosphotungstic acid-hematoxylin, Mallory's aniline blue and Foot's reticulum stains. Five of the lesions were sectioned serially. The vegetations varied in size from 0.5 mm. to 17 mm. in their greatest dimension. Fifteen (two acute and thirteen subacute) were superimposed on fibroplastic valvular deformities.

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6. Hadfield, G., and Garrod, L. P.: Recent Advances in Pathology, Philadelphia, P. Blakiston's Son & Co., 1934.

7. Baldasarri, V.: Centralbl. f. allg. Path. u. path. Anat. **20**:97, 1909.

8. Jaffé, R. H.: Virchows Arch. f. path. Anat. **287**:379, 1932.

OBSERVATIONS

Elastic and Collagenous Tissue.—With the simple hematoxylin-eosin stain, it was found impossible in the great majority of instances to be certain of the nature of the necrotic zone 1. The morphologic resemblance to simple platelet thrombi is certainly undeniable. With differential stains, however, isolated patches and strands of elastic and collagenous fibers were plainly visible within these "platelet" masses in many sections (figs. 1 and 2). Some were swollen and merged at one end with clear-cut wavy fibers, and on the other, with necrotic hazy shreds, finally shading off into an amorphous homogeneous granular material.

Frequently, solitary clumps of adult elastic and collagenous fibers, sometimes a single anuclear strand, were seen in a bed of necrotic débris near the periphery of the vegetation. The ends of these fibers were often frayed and ragged as if fragmented by the intense, widespread edema and necrobiosis and then forcibly pushed distalward from their original location (figs. 3 and 4). These separated foci of fibers stained quite like those elsewhere, e. g., the intact chordae tendineae.

Elastic or collagenous tissue was found in all but two of the vegetations. These were from hearts showing acute endocarditis and were composed simply of unidentifiable necrotic tissue and huge masses of bacteria. But even in these, collagenous fibers were seen fanning out into the vegetations from their bases. The edges of these fibers did not taper smoothly, as one might expect of granulation tissue, but were irregular and fragmented; so that one can hardly escape the impression that their distal ends originally extended farther into the vegetation—as in other instances—but were destroyed by the necrotic process.

The question naturally arises: May not these elastic or collagenous fibers be a part of the current reparative fibroplastic proliferation within the "thrombotic" mass? However, this seems hardly likely, since these same adult ragged strands of collagenous tissue may be found isolated near the periphery of acute vegetations (fig. 1) in which there has not been sufficient time for the formation of mature tissue of this character.[9] Furthermore, their anuclear nature and their complete separation from, or lack of continuity with, a nidus of fibroplastic proliferation, which nidus may be entirely absent if the infection is sufficiently virulent and recent, appear to prove that these fibers antedate the vegetation. The source of these fibers must therefore be the underlying fibroplastic deformity or—in the minority of cases—the fibroelastic and collagenous tissue of the normal valve. In other words, they evidence a destructive rather than a reparative process.

9. Maximow, A.: Beitr. z. path. Anat. u. z. allg. Path. **38**:301, 1905; Physiol. Rev. **4**:533, 1924; Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 141.

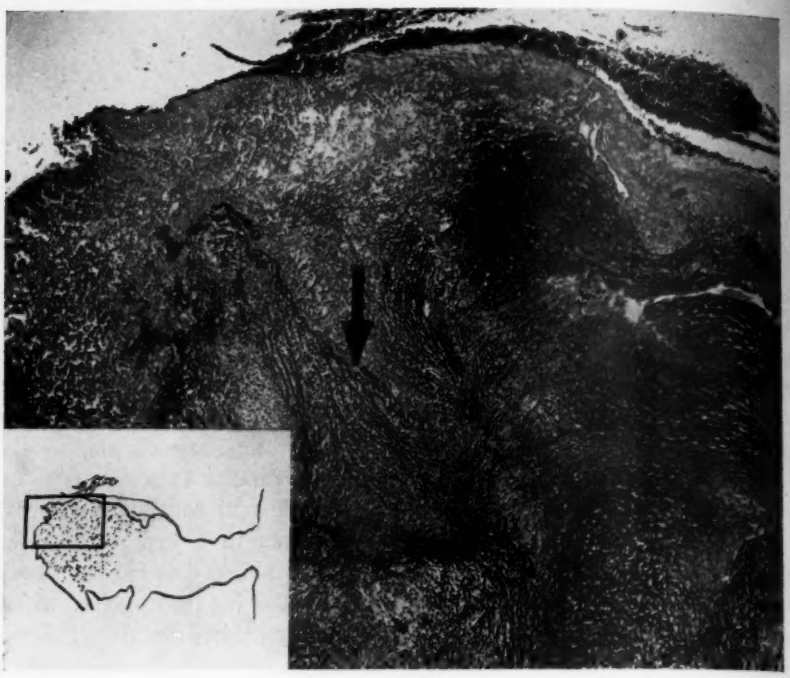

Fig. 1.—Vegetation of subacute endocarditis due to infection with Str. viridans, from mitral valve. There had been previous rheumatic deformity. This is a good example of crumbled, displaced, partially degenerated elastic strands and clumps squarely within a typical shaggy vegetation, ordinarily considered a simple thrombotic mass for the most part. Note that some of the fibers show partial loss of affinity for the elastica stain so as to resemble fibrin superficially (arrow). (Weigert's elastica Van Gieson stain; low power magnification.)

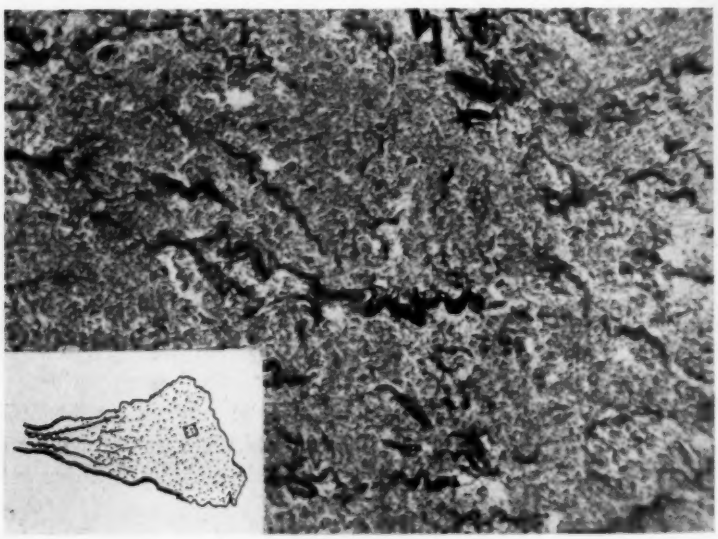

Fig. 2.—Acute endocarditis of the tricuspid valve due to infection with a hemolytic strain of Staphylococcus aureus (condition of five days' duration, clinically). There had been no previous apparent rheumatic involvement. Note the haphazard distribution of apparently forcibly separated, fragmented, disrupted collagenous fibers in various states of preservation, lying in a bed of disintegrating blood cells and granular precipitate. This illustrates the destructive factor in the origin of vegetations from valvular components which bulge outward into the chamber. (Van Gieson stain; high power magnification.)

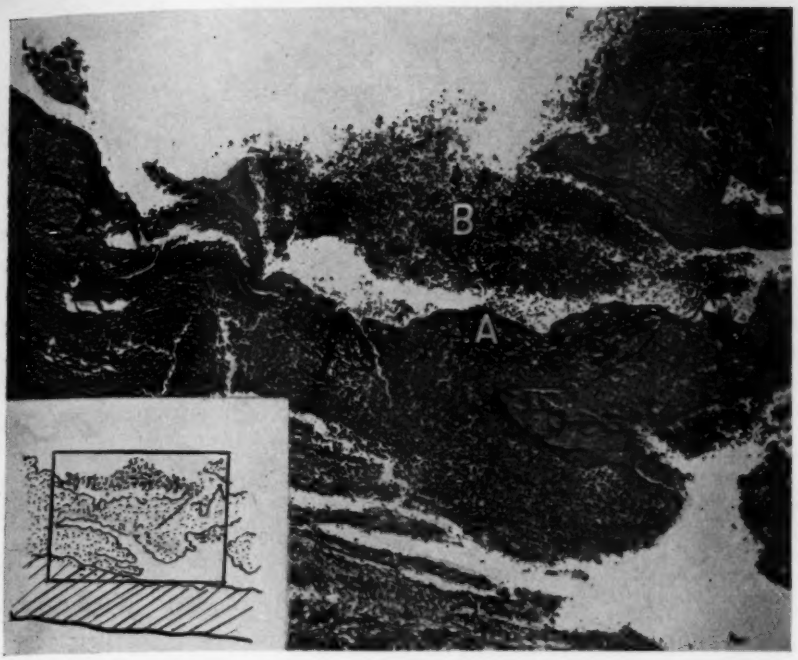

Fig. 3.—Vegetation of subacute endocarditis due to infection with Str. viridans, from the wall of the left auricle. Note that the "thrombotic mass" is overlaid in part by disrupted elastic fibers (*A*). Single strands (arrow) are seen as if actually forced through the débris, their distal ends lying free in the terminally deposited, well preserved blood (*B*). (Weigert's elastica Van Gieson stain; low power magnification.)

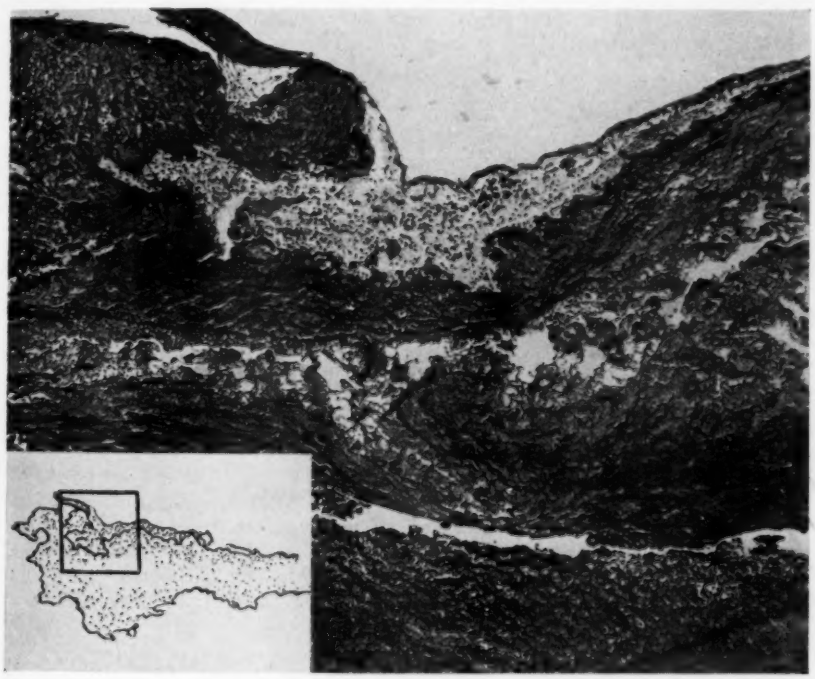

Fig. 4.—Vegetation of subacute endocarditis due to infection with Str. viridans, from mitral valve. Note the disrupted and distorted black elastic fibers at the periphery of the vegetation embedded in the necrobiotic débris and exudate. Also note the separation of elastic fibers as if forced apart by such material. (Weigert's elastica Van Gieson stain; low power magnification.)

These elastic and collagenous fibers may be easily and unequivocally differentiated from granulation tissue (and fibrin) by morphology, by their relationship to neighboring tissue, by their staining characteristics and by the duration of the lesions.[9] This was further confirmed by a study of sterile and infected thrombi as controls. Therefore, it may be concluded that these isolated adult fibers at the periphery of the vegetation appear to be definite evidence in favor of the view that these lesions arise from valvular tissue and to be distinctly contrary to the current

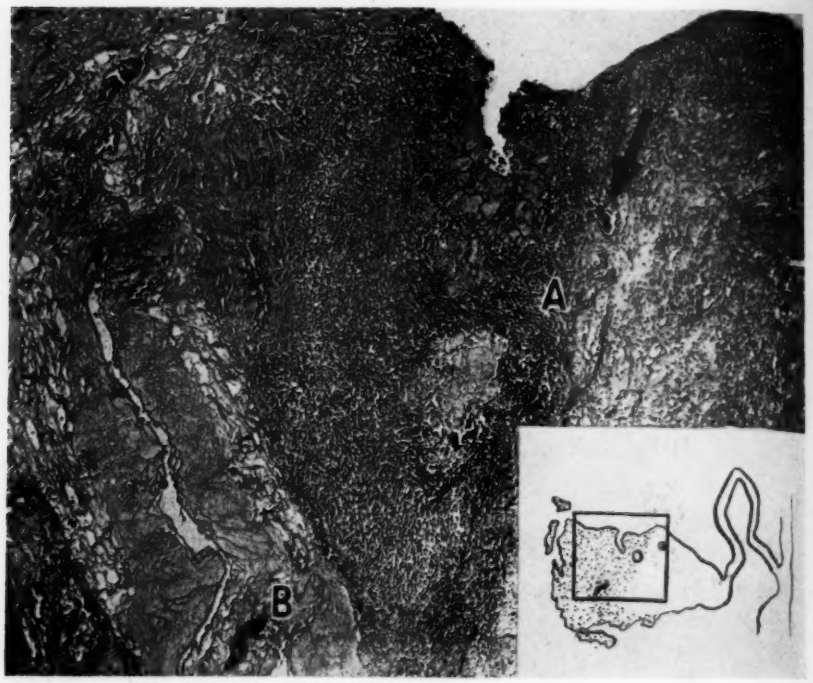

Fig. 5.—Vegetation of subacute endocarditis due to infection with Str. viridans, from mitral valve. There had been previous rheumatic deformity. Note so-called thrombotic mass extending from the left margin to *A*, consisting of necrobiotic valvular débris, fibrin, polymorphonuclear leukocytes, red blood cells, coagulated granular precipitate and displaced clumps and strands of elastic fibers. Note the proximity of blood vessels from the old fibroblastic deformity (arrow) to the vegetation. Such vessels, necrosed by the advancing ulcerative process, appear to be the source of the original and of additional blood elements within the vegetation. This is partly the reason for the absence of any characteristic arrangement such as one may find in vascular thrombi. Note the isolated clumps of elastic fibers within the fibrin mass (*B*). (Weigert's elastica Van Gieson stain; low power magnification.)

concept, according to which the material is deposited from the blood within the chambers.

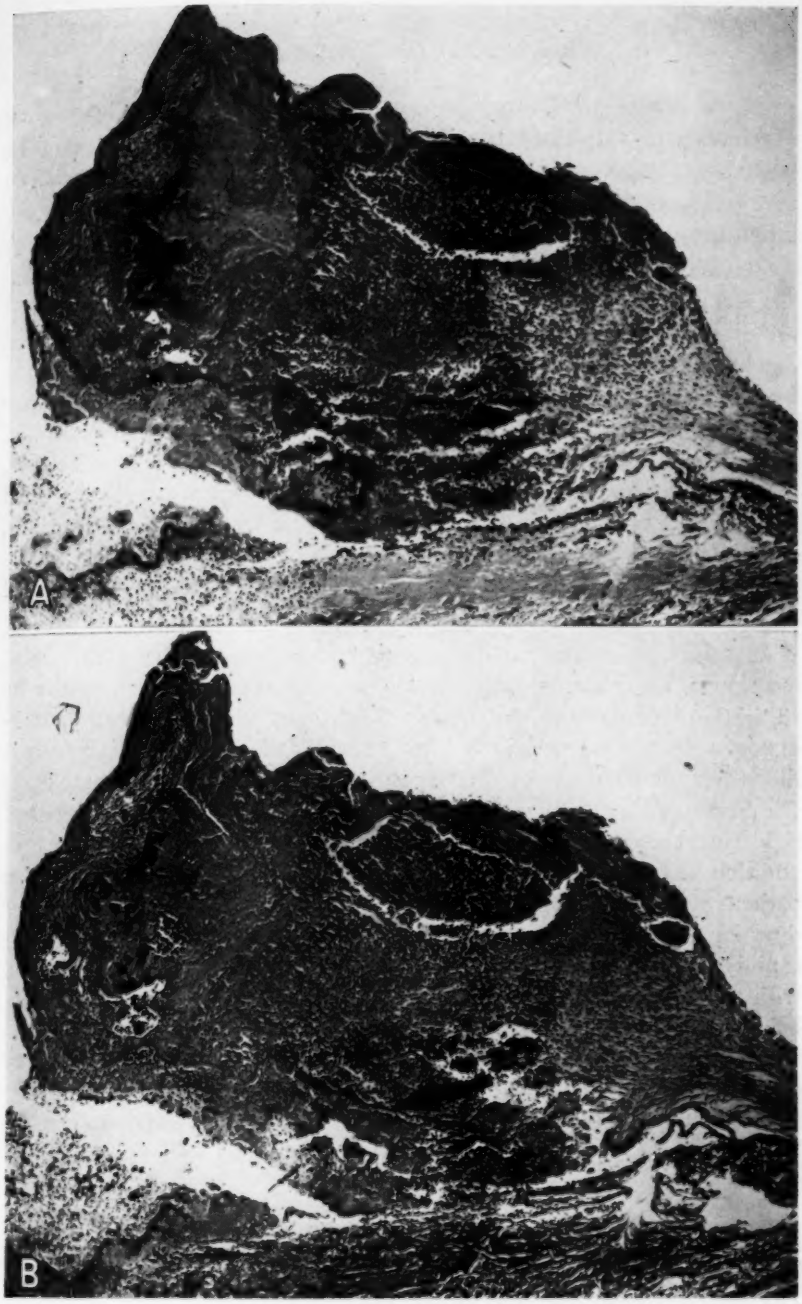

Fig. 6.—Vegetation of subacute endocarditis due to infection with Streptococcus viridans, from the outflow tract of the left ventricle. Note the divergence of the vegetation from the endocardium. In the section stained by Weigert's elastica Van Gieson stain (*B*), a strand of isolated elastic fibers (arrow) is seen within the "thrombotic mass" as if forced upward by the underlying necrobiotic débris and exudate. The section stained with hematoxylin and eosin (*A*) gives no hint as to the presence of such displaced fibers.

Vascularity.—Capillarization was seen directly within the body of all vegetations except 2, which were described in the foregoing text. The latter may be accounted for by the overwhelming necrosis, which one may conclude destroyed the elastic and collagenous fibers as well as the capillaries which may have been present.

This observation requires further discussion. Inasmuch as Gross stated that normal valves are not vascularized, what is the source of these capillaries? In the first place, 15 of this series were superimposed on obvious preexisting valvular deformities. (This is approximately the ratio for superimposition of bacterial endocarditis found by Libman,[10] Thayer,[11] Blumer [12] and others.) It is, of course, well known that rheumatic valvular lesions are vascularized (Gross [13]). In such cases, then, it is reasonable to believe that the red and white blood cells, coagulable plasma (fibrin) and "platelets" come from these vessels and their offshoots.

In the remaining vegetations there was no apparent underlying fibroplastic deformity as far as one was able to judge from necrotic lesions. What, then, was the source of these vessels, since normal valves, as mentioned, are perhaps not vascularized? In answer to this, it may be stated that vascularization of a valve may be part and parcel of the inflammatory response to bacteria, just as it may be elsewhere. It is not as if the vegetation were suddenly capped onto the valve. Even in acute cases (duration of six weeks or less by general agreement) there is sufficient time for thin-walled capillaries to form. Proof for this statement, in addition to the data included herewith, is furnished in valves from patients suffering the first attack of acute rheumatic fever—of six weeks' duration or less. In these Gross and Friedberg found distinct hypercapillarization throughout the valve leaflet. It is interesting in connection with this question of vascularity to recall that Von Glahn and Pappenheimer [14] expressed the belief that acute rheumatic endocarditis precedes all bacterial endocarditides. If this is so, the vascularity might be accounted for by this rheumatic process. Furthermore, Clawson [15] and also Bell and Hartzell [16] stated that there is diffuse inflammation of the leaflet in the early stages of bacterial endocarditis. The possibility of

10. Libman, E.: J. A. M. A. **80**:813, 1923.

11. Thayer, W. S.: Johns Hopkins Hosp. Rep. **22**:1, 1926.

12. Blumer, G.: Medicine **2**:105, 1923.

13. Gross, L., and Friedberg, C. K.: Am. J. Path. **12**:855, 1936.

14. Von Glahn, W. C., and Pappenheimer, A. M.: Arch. Int. Med. **55**:173, 1935.

15. Clawson, B. J.: Arch. Int. Med. **33**:157, 1924.

16. Clawson, B. J.; Bell, E. T., and Hartzell, T. B.: Am. J. Path. **2**:193, 1926.

the formation of superficial capillary sprouts from the endothelium of the surface of the valves must also be definitely reckoned with. In short, there is abundant evidence demonstrating that valves with bacterial endocarditis become vascularized even when there has been no apparent gross antecedent fibroplastic deformity. It is accordingly maintained that these vessels are the source of the red and white blood cells, coagulable plasma (fibrin) and "platelets" that may be found beneath the layer of bacteria. Furthermore, inasmuch as indisputably valvular

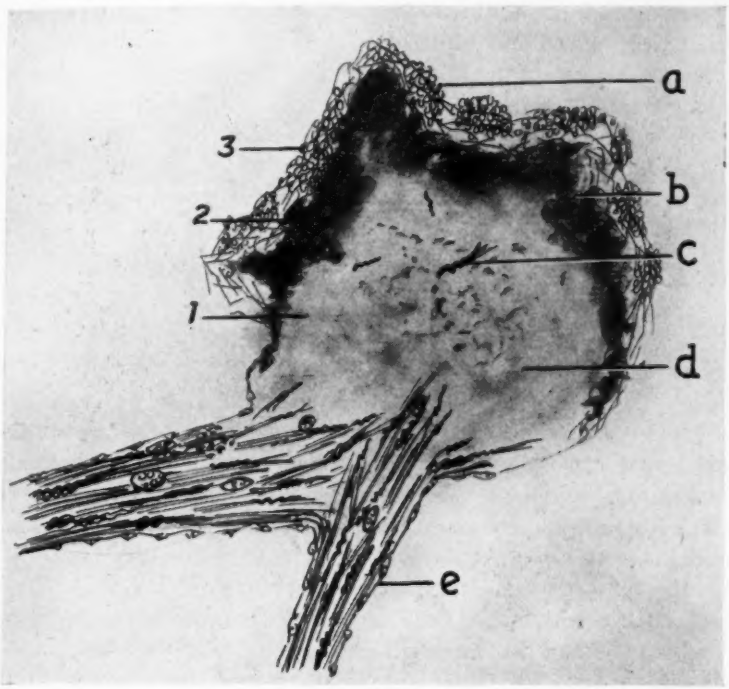

Fig. 7.—Diagrammatic representation of a typical bacterial vegetation. *1, 2* and *3* indicate zones 1, *2* and *3*, respectively; *a* indicates a superficial thrombus from blood within cardiac chambers; *b*, bacteria; *c*, collagenous fibers; *d*, necrotic collagenous fibers, blood cells and fibrin; v, chordae tendineae.

elastic and collagenous tissue is found overlying these blood elements, one may assume from this fact that these elements are not deposited in thrombotic fashion from the blood stream flowing over the valve but are derived from the various constituents of the inflamed or deformed valve.

"Platelet Mass."—The necrotic zone 1 beneath the bacteria is generally considered to be composed of a platelet mass to a great extent

(Gross and Fried;[16a] MacCallum;[4] Kaufman;[17] Clawson,[15] and others). However, it must be emphasized that this is predominantly a necrotic zone. Therefore, it does not seem justifiable to describe a more or less homogeneous granular material as a mass of platelets in the face of the very palpable possibility that that material may be the residue of necrobiosis and therefore truly unidentifiable. However, one may perhaps judge the nature of this material from the character of the surrounding tissue. As was mentioned, elastic and collagenous fibers were frequently seen radiating and finally disappearing into the necrotic mass to appear again in scattered random areas (figs. 3 and 4). Between these separated fibers, red and white blood cells were seen also merging with this homogeneous substance. Therefore, it seems more reasonable to conclude that this granular material represents fibrous tissue and blood elements which have undergone necrobiosis rather than simply assentially a "platelet mass," as it is currently regarded. This tends further to refute the current concept of the nature of the bacterial vegetation.

The remainder of the vegetation consists distally of a rim of bacteria and a layer of simple thrombotic material, apparently deposited from the blood as it flows over the valve. This last zone does not appear to be an intrinsic part of the lesion, however. One is often impressed with the good state of preservation of this layer—as if it constituted a more or less terminal deposit.

Bacterial Layer.—The frequency with which a band of bacteria is found near the periphery of the vegetation, both in human and experimental endocarditides (Rosenow[18]), is not reconcilable with the concept that the lesion is a thrombus (Jaffé[8]) deposited from the blood of the chamber. If this concept were a fact, one would expect the thrombus to overlie the organisms, inasmuch as they are, of course, assumed to precede the vegetation. Yet, the major portion of the vegetation generally underlies the bacteria. In defense, Perry[1] maintained that the organisms have originally been at the base but have lost their affinity for stains. If this is true, one wonders why there is no stratification showing the transition from the dead bacteria proximally to more viable ones peripherally instead of the abrupt rim so often seen at the surface.

In concluding, it is believed that the evidence that the bacterial vegetation is not a simple thrombus deposited from blood flowing over the valve concerns an issue greater than that of the mere morphologic nicety. For example, on this point may rest supporting evidence for an important, well recognized concept, namely, that tissue immunity in the broad con-

16a. Gross, L., and Fried, B. M.: Am. J. Path. **13**:769, 1937.

17. Kaufman, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, pp. 25-37.

18. Rosenow, E. C.: J. Infect. Dis. **7**:411, 1910; **11**:210, 1912.

notation of allergy [19] is a factor in the production of bacterial endocarditis. If one is permitted the luxury of speculatively integrating morphologic observations with vital phenomena, one is led to believe that the marked necrosis and edema, with ripping and separation of originally closely packed elastic and collagenous fibers, are strongly reminiscent of a response to an altered local tissue reactivity.

SUMMARY

The structure of the vegetations in 24 cases of acute and subacute bacterial endocarditis was studied with the aid of differential connective tissue stains.

In agreement with current descriptions, the bulk of each of these vegetations was found generally to consist of a necrotic zone beneath a layer of bacteria.

Isolated clumps, fragmented strands and segmented bits of typical adult elastic and collagenous tissue, easily distinguished from granulation tissue or fibrin, were found scattered through this necrotic zone in both acute and subacute vegetations. *These fibers are considered evidence of a destructive rather than of a reparative process.*

The question as to whether or not this necrotic zone is really essentially a platelet mass, in accordance with the current concept, is discussed on the basis of morphologic observations.

It is concluded, contrary to the long established current concept, that the bulk of a vegetation of acute or of subacute bacterial endocarditis is derived from components of inflamed and fibroplastically deformed valves and is not derived from blood flowing over the valves.

1 East 100th Street, New York City.

19. Semsroth, K., and Koch, R.: Arch. Path. **10**:867, 1930. Wadsworth, A. B.: J. M. Research **39**:279, 1919. Derick, C. L., and Swift, H. F.: Proc. Soc. Exper. Biol. & Med. **25**:222, 1922. Kinsella, R. A., and Sherburne, E. C.: J. A. M. A. **80**:1643, 1923. Wright, A. D.: J. Path. & Bact. **29**:5, 1926. Swift, H. F.: Am. Heart J. **3**:629, 1928.

PROGRESSIVE ALCOHOLIC CIRRHOSIS

A CLINICAL AND PATHOLOGIC STUDY OF SIXTY-EIGHT CASES

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AND
WENDELL A. MORGAN, M.D.
LOS ANGELES

Interest in Laënnec's cirrhosis continues, owing, no doubt, to the importance of the condition as a disease and to the fact that the etiologic factors are still in question. The old controversy as to the role of alcohol in cirrhosis continues. Attempts to produce cirrhosis in animals by the use of alcohol have almost invariably failed. Physiologists and experimental pathologists are, on the whole, opposed to the idea that alcohol is a direct cause of cirrhosis. Mallory [1] stated that after thirty-six years of experimentation on alcoholic cirrhosis he, like other investigators, had ruled out ethyl alcohol as the cause. Boles and Clark,[2] from a study of the records of 4,000 autopsies made at the Philadelphia General Hospital from 1933 to 1935, concluded that alcohol cannot be regarded as a specific factor in the causation of cirrhosis. They suggested abandonment of the term "alcoholic cirrhosis."

It is generally agreed that ethyl alcohol is not a strong hepatic poison like arsenic or phosphorus, nor is it so active in producing necrosis of the liver as chloroform and carbon tetrachloride. Nevertheless, when alcohol is injected in doses of 0.1 cc. directly into the portal circulation, it produces localized necroses of the liver, as shown by Ogata [3] and more recently by Cameron, Karunaratne and Thomas.[4] Similar changes, but with massive infarct-like necroses, are produced by the injection of chloroform (Whipple and Sperry; [5] Schultz, Hall and Baker [6]) and by the injection of carbon tetrachloride (Schultz and Marx; [7] Cameron,

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From the departments of pathology of the Los Angeles County Hospital and the School of Medicine of the University of Southern California.

1. Mallory, F. B.: Am. J. Path. **9**:557, 1933.
2. Boles, R. S., and Clark, J. H.: J. A. M. A. **107**:1200, 1936.
3. Ogata, S.: J. M. Research **40**:103, 1919.
4. Cameron, G. R.; Karunaratne, W. A. E., and Thomas, J. C.: J. Path. & Bact. **44**:297, 1937.
5. Whipple, G. H., and Sperry, J. A.: Bull. Johns Hopkins Hosp. **20**:278, 1909.
6. Schultz, E. W.; Hall, E. M., and Baker, H. V.: J. M. Research **44**:207, 1923.
7. Schultz, E. W., and Marx, A.: Am. J. Trop. Med. **4**:469, 1924.

Karunaratne and Thomas [4]). Cameron and his associates studied these changes carefully and expressed the belief that such lesions are due to a direct toxic action of the poison on the liver cells. They have proposed the term "toxic infarction," which is an apt one.

Granted that alcohol, chloroform and carbon tetrachloride produce hepatic necrosis under the conditions outlined, it does not follow necessarily that cirrhosis results from the healing of such lesions. As already noted, true Laënnec's cirrhosis had not resulted from experiments in which alcohol was given to animals, although some periportal proliferation of fibrous tissue has been reported by several investigators. Whipple and Sperry [5] failed to find cirrhosis following prolonged chloroform anesthesia (two to three hours) in dogs although central necrosis of the hepatic lobules inevitably resulted from the effects of the anesthetic. Several of the dogs died from acute hepatic necrosis within a period of two to seven days after their anesthesia. In the dogs that survived the administration of choloroform, complete restoration of the hepatic lobules occurred by regeneration of the liver cells.

Herter and Williams,[8] however, reported that definite cirrhosis occurred when dogs were anesthetized with chloroform three times per week. One dog received a total of eighteen, another a total of forty-nine, inhalations. The animals lived five and eight months, respectively. Data as regards carbon tetrachloride cirrhosis are still more convincing because of the work of Lamson and Wing,[9] Bollman and Mann [10] and Cameron and Karunaratne.[11] The latter found well marked cirrhosis of a permanent type in rats that had received from twenty-eight to forty doses of 0.1 cc. of carbon tetrachloride at the rate of two a week. When only sixteen to twenty-one doses were given, the fibrosis was only temporary and usually disappeared within two to three weeks. Cameron and Karunaratne pointed out that cirrhosis results from injections of carbon tetrachloride only when the following conditions are fulfilled: 1. A dose greater than the minimal toxic dose for the liver must be used. 2. It must be administered either continuously or at short intervals over a prolonged period. 3. The intervals between doses must be sufficiently short to avoid complete repair of the damage produced by the preceding dose. Herter and Williams [8] seem to have fulfilled these requirements in producing chloroform cirrhosis in dogs. Von Glahn, Flinn and Keim [12] showed recently in rabbits fed lead,

8. Herter, C. A., and Williams, W. R.: Proc. Soc. Exper. Biol. & Med. **3**: 23, 1905.

9. Lamson, P. D., and Wing, R.: J. Pharmacol. & Exper. Therap. **29**: 191, 1926.

10. Bollman, J. L., and Mann, F. C.: Ann. Int. Med. **9**:617, 1935.

11. Cameron, G. R., and Karunaratne, W. A. E.: J. Path. & Bact. **42**:1, 1936.

12. Von Glahn, W. C.; Flinn, F. B., and Keim, W. F.: Arch. Path. **25**: 488, 1938.

copper and sodium arsenates an incidence of cirrhosis above 90 per cent. The animals received 5.6 to 12 mg. of one of the aforenamed salts daily for periods ranging from one hundred to two hundred days. Here again the principle of many, closely timed injuries to the liver over a considerable period resulted in cirrhosis in a very high percentage of the animals.

Alcohol, which is less toxic for the animal liver than either chloroform or carbon tetrachloride, probably has to be administered in correspondingly larger doses over a long period in order to produce severe changes in the liver. More recently evidence has been accumulating which indicates that for man, at least, the body and more especially the liver must be in a state of altered metabolism before cirrhosis will result from heavy drinking of alcoholic liquor. That abnormal changes take place in metabolism, more specifically in the utilization of carbohydrates, fats and proteins, in the patient who drinks a pint of whisky per day for twenty or twenty-five years is well known. That the liver suffers from alcoholic overindulgence is evident from the great increase in fat, an increase generally accepted clinically and proved experimentally to be due to alcohol (Ruge;[13] Friedenwald;[14] Fahr[15]). The liver of the consumer of alcohol is also very low in glycogen content (LeCount and Singer[16]). It is probably not only the toxicity of alcohol itself but also the increased susceptibility of the already damaged cells of the liver to a mild hepatic poison under conditions of changed carbohydrate metabolism, lowered intake of food and deficiency in certain vitamins that makes possible the changes seen in cirrhosis. Furthermore, there is some evidence for an individual idiosyncrasy toward alcohol, as there is toward many drugs, since cirrhosis develops in only 5 to 6 per cent of persons addicted to the use of alcoholic beverages.

There can be no doubt that portal cirrhosis is produced by a considerable number of agents (Moon[17]). Studies of Laënnec's cirrhosis in the chronic form ordinarily show an alcoholic history in but 25 (Evans and Gray[18]) to 35 per cent (Boles and Clark[2]) of the cases. Does this necessarily mean that there is no true alcoholic cirrhosis? Or does it indicate simply that investigators have failed to recognize the alcoholic group because toxic agents other than alcohol are capable of producing a portal type of cirrhosis which in the late stages is not distinguishable from the alcoholic variety? We believe that the latter is the case. We maintain that the term "alcoholic cirrhosis" is fully justi-

13. Ruge, P.: Virchows Arch. f. path. Anat. **49**:252, 1870.
14. Friedenwald, J.: J. A. M. A. **45**:780, 1905.
15. Fahr, T.: Verhandl. d. deutsch. path. Gesellsch. **13**:163, 1909.
16. LeCount, E. R., and Singer, H. A.: Arch. Path. **1**:84, 1926.
17. Moon, V. H.: Arch. Path. **18**:381, 1934.
18. Evans, N., and Gray, P. A.: J. A. M. A. **110**:1159, 1938.

fiable. In the following pages we shall analyze a group of cases in which we believe the true picture of alcoholic cirrhosis in the early, progressive stages was presented.

Evans and Gray [18] recently published a study of 217 cases of Laënnec's cirrhosis which were observed among 17,000 autopsies at the Los Angeles County Hospital. They were especially interested in the relation of alcohol to cirrhosis and showed a definite increase in the incidence of this disease beginning in 1932 soon after the repeal of the national prohibition law. Our cases are taken from the same group of autopsies as were the cases of Evans and Gray; however, some 2,000 autopsies from May 1, 1937, to May 1, 1938, have been included in our series that were not in theirs. None of our cases goes back beyond autopsy 7,000, since sufficient data could not be assembled from the earlier cases on which to separate them clearly into our group. The two subgroups overlap sufficiently, however, for us to use the larger series of 217 cases studied by Evans and Gray for the purposes of comparison.

Our 68 cases were selected as instances of the progressive, or active, type of alcoholic cirrhosis as described by Hall and Ophüls.[19] This condition may be conveniently designated as subacute alcoholic cirrhosis. The liver is enlarged, the weight ranging from 2,000 to 5,000 Gm., and is usually but not always fatty. Eighty-five per cent of the patients were consumers of alcohol in some form. Fifty-one patients, or 75 per cent, were shown to have chronic alcoholism; i. e., they were "heavy drinkers."

Other characteristics of the liver in subacute alcoholic cirrhosis are as follows: The surfaces of the organ are smooth or finely granular rather than the hobnail type seen in chronic cirrhosis. The fibrosis is generally less severe than in the chronic type, while cellular or relatively cellular connective tissue proliferation is found in the portal areas. Necrosis of liver cells is still present, in many cases being quite marked. Fibroblastic cells may usually be seen proliferating about the dead hepatic cells. Polymorphonuclear leukocytes are frequently present along with the lymphocytic cells which infiltrate the periportal connective tissue.

This group of patients were, then, quite largely suffering from alcoholism. The livers were mostly of the large, pale yellow fatty type, with the connective tissue actively proliferating about disintegrating hepatic cells. The picture was that of early or subacute alcoholic cirrhosis.

ANALYSIS OF CLINICAL DATA

These 68 cases were selected from among autopsies 7,000 to 20,000 at the Los Angeles County Hospital. The 217 cases selected by Evans and Gray include some of ours and many additional cases of alcoholic cirrhosis of the chronic hobnail type.

19. Hall, E. M., and Ophüls, W.: Am. J. Path. **1**:477, 1925.

Race.—Caucasians predominate with 57 patients, or 85 per cent. Ethiopians are next most numerous with 6, or 8.8 per cent, and then Mexicans with 5, or 7.35 per cent.

Sex.—As would be expected, males are found to exceed females nearly 2 to 1, the actual numbers being 44 and 24. The average age at death for the whole group is 46.8 years, as contrasted with 60 years in the larger group (Evans and Gray). Figure 1 is a graph comparing our series with that of Evans and Gray in respect to the ages at death, by decades.

The youngest patient in our group was 24 years old at the time of death; the oldest was 75. Only 4 patients died in each of the corresponding decades. It is evident from figure 1 that in cases of subacute alcoholic cirrhosis death occurs mainly between the ages of 35 and 55 while in cases of chronic cirrhosis it occurs about ten years later. In the group with the chronic condition the "ages of death" also show wider

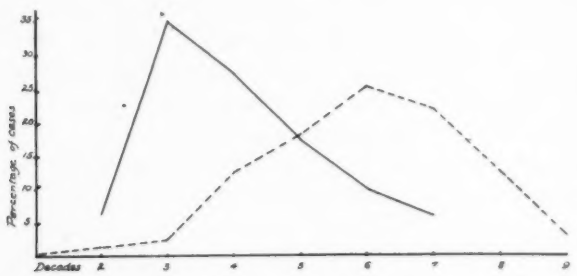

Fig. 1.—Graph comparing the distribution of ages at death, in decades, in the authors' cases (solid line) with that in the cases of Evans and Gray (broken line).

distribution. Heavy drinking is not frequently encountered before the twentieth or after the seventieth year. We cannot agree with Connor [20] in his statement that cirrhosis usually develops between the fifth and sixth decades. In the cases in the Los Angeles County Hospital death intervenes at that time or earlier.

History of Alcoholism.—Fifty-one, or 75 per cent, of the 68 patients were sufferers from chronic alcoholism, most of them having imbibed large quantities of whisky, often as much as a pint (473 cc.) or even a quart (946 cc.) per day, over a period of five to twenty-five years. A few drank considerable quantities of wine, usually one to two quarts daily. Six patients were classified as "moderate drinkers" because of insufficient data. Three of these, we believe, had chronic alcoholism. In 10 cases no record as to alcoholic habits was made on the hospital

20. Connor, C. L.: Am. J. Path. **14**:347. 1938.

charts. Ten of the 51 patients had one or another form of alcoholic psychosis. Seven had either pellagra or alcoholic neuritis.

Of the 10 patients with no record of having consumed alcoholic liquors, all but a single patient had severe acute infections. Most of them died within a few hours after entering the hospital. Three were in coma from the time of entry to the time of death. The only patient of this group who had no infection died of congestive heart failure. The histories of all but the last patient were necessarily deficient, and save in the 1 case the omission of data regarding the consumption of alcohol is probably justified.

The patients in this series were not selected because of their alcoholism but on the basis of the gross anatomic and histologic changes in their livers. Since 80 per cent of the whole group were consumers of alcoholic liquors, it seems logical to assume that 80 per cent of the patients whose alcoholic habits were not recorded were also consumers of alcoholic liquors. If the foregoing assumption is correct, 90 per cent of the entire group suffered from alcoholism.

Wassermann Reaction.—A positive Wassermann reaction was recorded in 12 cases, or 17.6 per cent. A negative Wassermann reaction was found in 39 cases. In 17 cases no data on this reaction were available. In only a single case in which the Wassermann reaction was strongly positive was there no record of alcoholism. Evans and Gray [18] reported syphilis present in only 12 per cent of their cases. The question naturally arises as to whether or not syphilis plays a part in the production of alcoholic cirrhosis. Our series of cases suggests an etiologic relationship. The most extreme fibrosis encountered in this group was associated in a number of instances with a positive Wassermann reaction (fig. 2). Such a reaction was seen in 50 per cent of the cases in which the Wassermann reaction was positive and in only 20 per cent of the remainder. Schumacher [21] emphasized the relation of syphilis to the production of a portal type of cirrhosis.

Jaundice, Ascites and Hemorrhage.—Jaundice was noted in 34 cases (50 per cent) of the series. In 24 cases the icteric index was 50 units or above; in some it was as high as 200 units. This figure (50 per cent) is considerably higher than that obtained for the mixed group (Evans and Gray), which was 29.5 per cent. It is to be expected that a group of patients suffering from a subacute type of cirrhosis in which hepatic necrosis and acute infection are prominent factors would exhibit a higher incidence of jaundice than would be found in a group suffering mainly from a more chronic form of hepatitis. Previous attacks of jaundice were recorded for 6 patients. These attacks occurred about six months

21. Schumacher, G. A.: Am. J. M. Sc. **194**:693, 1937.

to two years before the last entry into the hospital except in a single patient who reported that an attack had occurred fourteen years previously.

Ascites was present in 41 patients, or 60.3 per cent. It is interesting that Evans and Gray [18] found ascites in 131 patients in their larger group of 217, or in 60.3 per cent. In 11 of our patients, ascites had been found previously—in 8 of these within six months to one year. One of the remaining 3 patients had had ascites two years before, and another, five

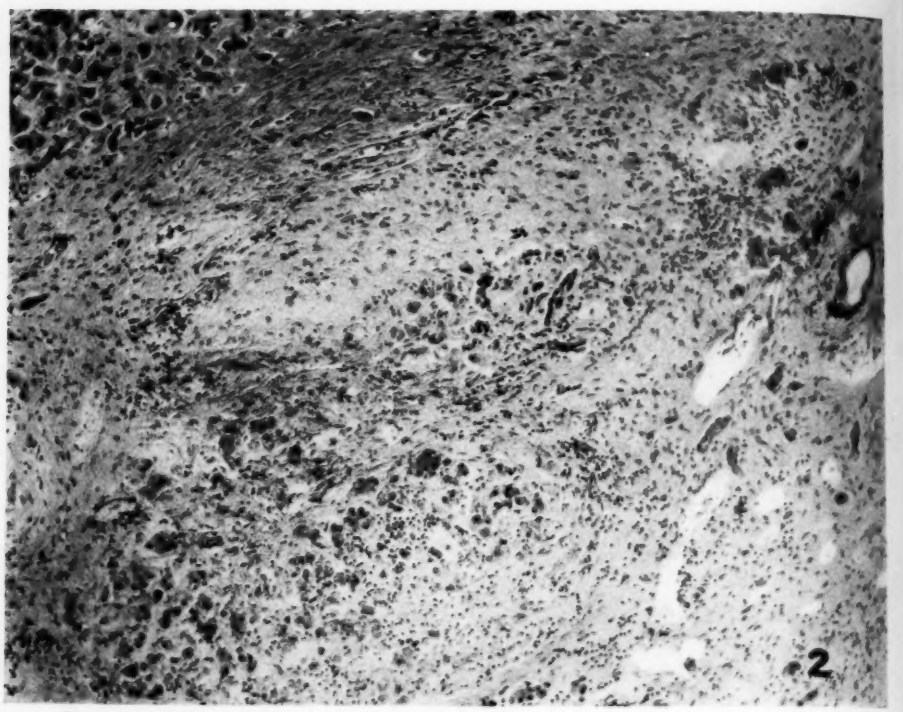

Fig. 2.—The patient was an Ethiopian woman aged 44. She had chronic alcoholism and a positive Wassermann reaction. The liver weighed 2,550 Gm. Fibrosis was marked. The photomicrograph (low power) shows dense bands of fibrous tissue, which are not confined to the periportal spaces. The pale areas are composed of a less dense connective tissue. Note the small groups of degenerating liver cells. Only a few new bile ducts are seen in this section. Hematoxylin and eosin; × 65.

years previously, with enlargement of the liver; in the third abdominal swelling had been present for years.

Varices of the esophagus with gastric hemorrhage were found in 24 (35.3 per cent). Varices were recorded in a few instances without

hemorrhage. Hemorrhage was fatal in 14 instances, or 20 per cent, which is a higher figure than that reported by Evans and Gray, 13.9 per cent.

Bloomfield [22] recently emphasized the importance of previous attacks of jaundice or of hepatitis in cirrhosis. Eleven of the patients in our series had had earlier attacks of jaundice, and 14 gave evidence of previous hepatic disturbance. The data on these attacks are summarized in table 1.

The correct clinical diagnosis was made in 36 instances, or 52.9 per cent; the diagnosis was partially correct in 12 cases, or 17.6 per cent, and incorrect in 20 cases, or 29.4 per cent.

TABLE 1.—*Findings Suggesting Previous Attacks of Hepatitis*

Condition	Patients
Attacks of epigastric pain or of pain in the right upper quadrant of the abdomen (6 months to 7 years)	6
Palpable or tender liver or both (6 months to 5 years)	5
Hematemesis (with epigastric pain in 2 cases *), one 7 years previously	3
Fever and vomiting intermittently for 3 years	1
Indigestion, jaundice and ascites (6 months previously)	1
	16

* Also listed under first item (total number of patients—14).

TABLE 2.—*Liver Weights*

Wt. Range, Gm.	Number
Below 2,000	5
2,000-3,000	39
3,000-4,000	15
4,000-5,000	6

ANALYSIS OF GROSS AND MICROSCOPIC CHANGES IN THE LIVER

Weight of the Liver.—The average weight of the liver in the 68 cases was 2,760 Gm. We have arbitrarily considered 2,000 Gm. the lower limit of hepatic weight for the subacute type of cirrhosis, though no hard and fast rule can be laid down. In a few of our cases, the weight of the liver fell below this figure. The smallest liver weighed 1,400 Gm.; 4 others ranged from 1,800 to 1,950 Gm. The largest liver in the series weighed 5,000 Gm.

The weight of the spleen was recorded in 66 of the 68 cases, the average being 360 Gm. This is approximately double the weight of the normal adult spleen. The increase in size was no doubt to a large

22. Bloomfield, A. L.: Am. J. M. Sc. **195**:429, 1938.

extent the result of chronic passive congestion. The organ was usually said to be firmer than normal. The exceptions were found in cases complicated by acute infection. Microscopically, there was diffuse fibrosis and usually there was reduction in the amount of lymphoid tissue.

In 40 instances, or 61.5 per cent, the surface of the liver was described as varying from smooth to finely granular, while in 25 instances, or 38 per cent, it was described as varying from roughly granular to nodular. The latter group, except for the enlargement of the organs, would appear to fall into the group of cases of the more chronic forms of Laënnec's cirrhosis. In 3 cases, the surface of the liver was not described.

Hepatic Fibrosis.—The relative amount of fibrosis in the various livers was estimated by microscopic examination and recorded as slight in 3 cases (4.4 per cent), moderate in 14 (20.6 per cent), marked in 32 (47 per cent) and extreme in 19 (or 28 per cent). All of the cases in which the Wassermann reaction was positive fell into one or the other of the last two groups. The amount of fibrous tissue proliferation in the general run of our cases seemed on the whole to be somewhat reduced in comparison with that seen in cases of the more chronic types of hepatitis. In distribution it was mainly periportal but not necessarily so. Of greater importance was the kind, or the maturity, of the connective tissue. Among the cases of subacute alcoholic cirrhosis we found 15 cases (22 per cent) in which it was classified as cellular; 11 (16.2 per cent) in which it was classified as moderately cellular; 37 (54.4 per cent) in which it was said to vary from moderately cellular to dense, and only 5 cases (7.4 per cent) in which it was designated as dense. Certainly the number of instances in which the connective tissue was cellular or moderately cellular (38 per cent) is greatly in excess of that noted for chronic atrophic cirrhosis (fig. 3). The largest group, 54.4 per cent, in spite of greater maturity, still showed evidence of fibroblastic proliferation, especially at the junction of fibrous tissue and liver cells and more especially about degenerating or necrotizing cells. The fact that fibrocytes are almost invariably found invading areas containing degenerating liver cells caused Hall and Ophüls [19] to suggest that toxic substances which destroy the less resistant liver cells serve only to stimulate the more hardy connective tissue to active proliferation. References have been cited to show that simple destruction of liver tissue by a variety of methods does not, as a rule, lead to permanent fibrosis. Ordinarily the liver tissue regenerates, and temporary scarring later completely disappears.

Considerable variability was noted in the amount of cellular infiltration of the periportal connective tissue. In most instances, the greater proportion of cells consisted of small lymphocytes as in chronic cirrhosis.

In the cases of subacute cirrhosis, however, almost regularly a moderate number of polymorphonuclear leukocytes were present as well. In a few cases they were quite abundant (fig. 4), exceeding the number of lymphocytes.

Necrosis of the Liver Cells.—A prominent characteristic of the subacute type of cirrhosis is the presence of hepatic necrosis. In the chronic stage of Laënnec's cirrhosis ordinarly one may search in vain for necrotic liver cells. Perhaps a few scattered cells caught within the connective

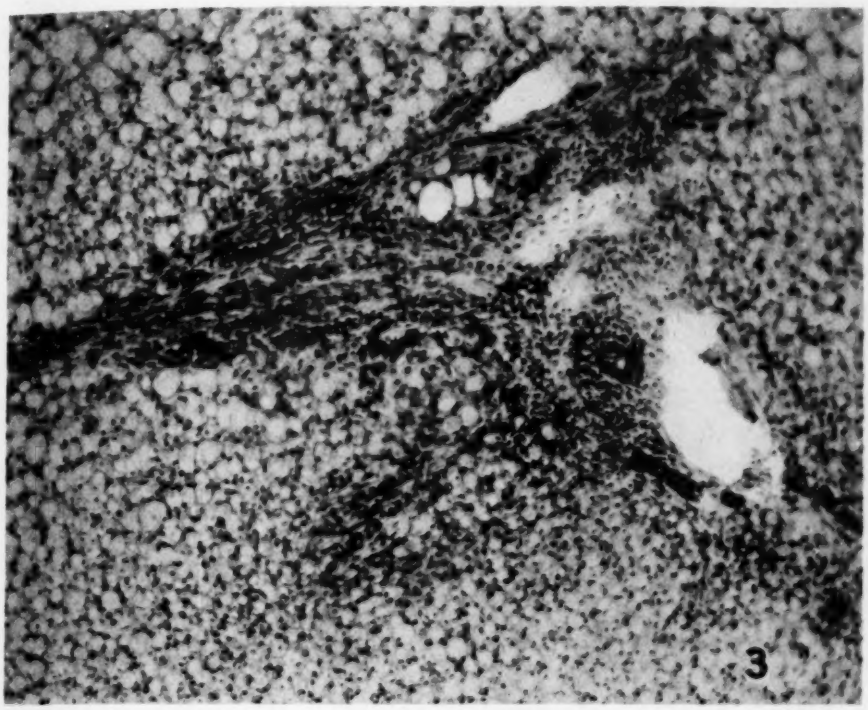

Fig. 3.—The patient was a Caucasian man aged 38 years, with chronic alcoholism. The liver weighed 2,080 Gm. The photomicrograph shows marked fatty infiltration of the liver, with cellular connective tissue growing out from the portal area into the surrounding parenchyma. Inflammatory cells infiltrate the connective tissue. Hematoxylin and eosin; × 120.

tissue appear atrophic or actually necrotic. This is probably largely mechanical, however, and not the direct result of toxic action. In 24 of our cases, or 35.8 per cent, occasional necrotic or degenerating cells were seen along the borders of the periportal fibrous areas. In 21 cases, or 31.8 per cent, there were a moderate number of necrotic cells; in 18 cases, or 27 per cent, groups of necrotic liver cells were seen not only in the periphery but also in various positions within the lobule (fig. 5).

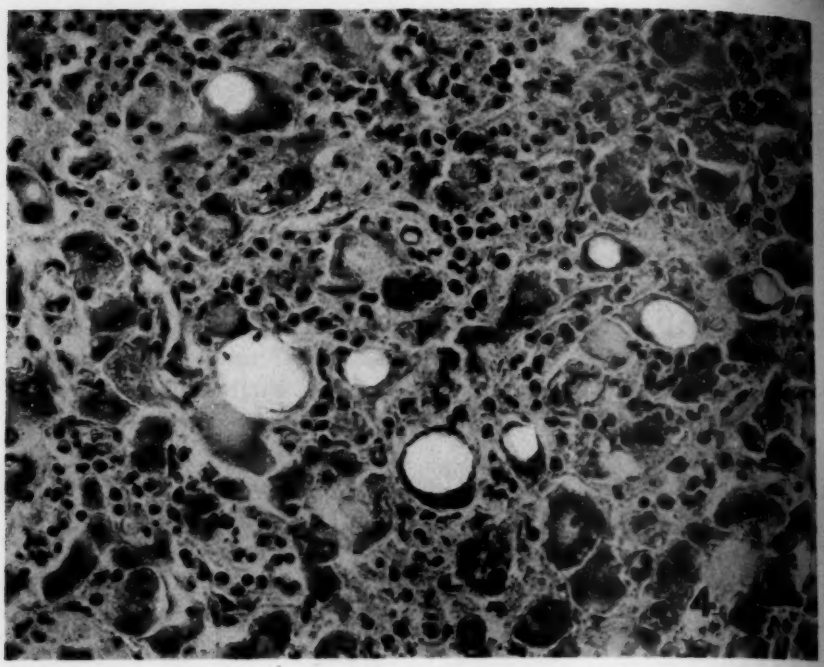

Fig. 4.—The patient was a Mexican man aged 39 years, markedly alcoholic. The liver weighed 3,300 Gm. The photomicrograph (high power) illustrates early proliferation of fibroblasts about necrotic liver cells. Many of the latter contain "hyalin." There is a diffuse infiltrate of inflammatory cells, many of which are polymorphonuclears. Hematoxylin and eosin; × 335.

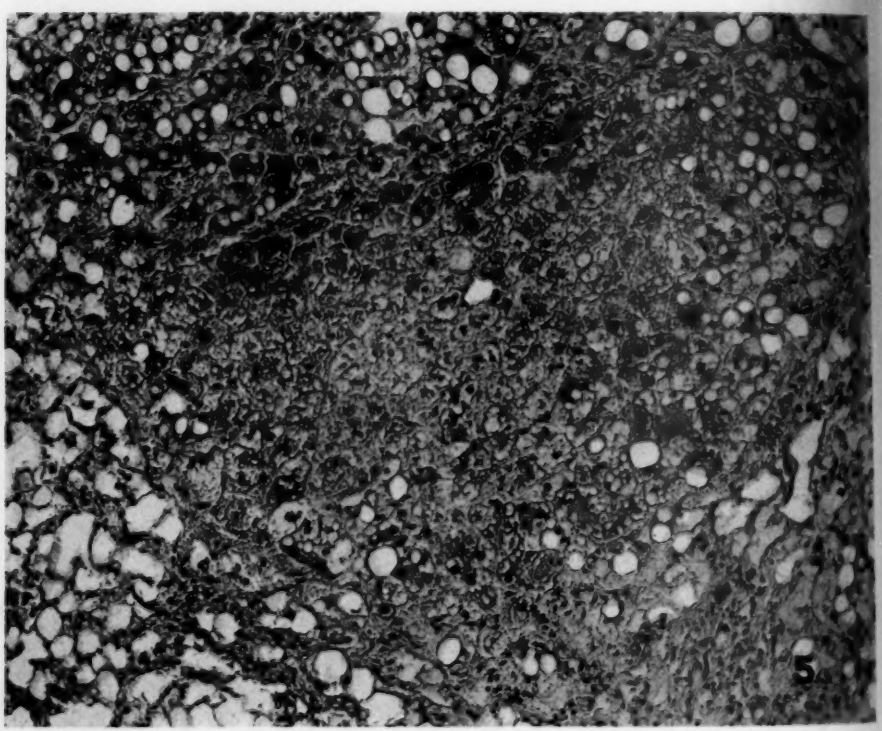

Fig. 5.—The patient was a Caucasian man aged 57, with chronic alcoholism. The liver was extremely fatty and weighed 5,000 Gm. The photomicrograph (low power) shows a large amount of fat, a large area of necrosis and a moderate increase of cellular fibrous tissue. Hematoxylin and eosin; × 100.

In a few cases the liver showed a marked degree of necrosis. In general, the earliest changes in the degenerating liver cells appear in the form of either nuclear fading or pyknosis accompanied by vacuolation of the cytoplasm. The latter is due usually to hydropic degeneration. The cytoplasm swells, and numerous small round or polygonal clear spaces appear. Later, the nucleus disappears, and the cells, which may become greatly swollen, disintegrate (fig. 6). Other cells exhibit a peculiar lumpy hyaline appearance of the cytoplasm, which seems to represent a type

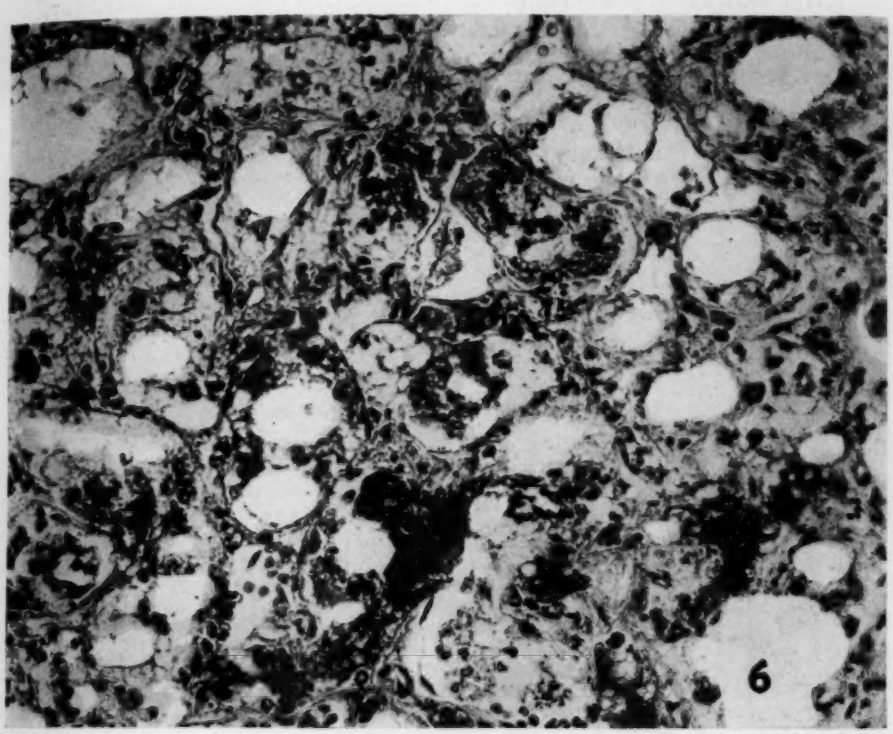

Fig. 6.—The patient was a Caucasian woman aged 39 years. She had chronic alcoholism and the Wassermann reaction was positive. The liver weighed 3,200 Gm. The photomicrograph (high power) shows a number of swollen, degenerating liver cells. Three large cells near the center contain masses of "hyalin" in their cytoplasm. Other cells show hydropic degeneration. Fibroblasts are beginning to appear about the degenerating cells. Polymorphonuclears are present. Methylene blue-eosin; × 335.

of coagulative necrosis. The hyalin stains more deeply with eosin than the granular parts of the cytoplasm. Karyolysis and pyknosis of nuclei frequently accompany these changes, occurring at times within the same cells. Mallory [23] first described the hyaline changes as specific for alco-

23. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911.

holic cirrhosis but does not so regard them at the present time. Fifty-five, or 80.88 per cent, of the livers in our series showed the "alcoholic" hyalin to some degree. In many instances it was abundantly evident (fig. 7). In 9 instances (13.2 per cent) the presence of hyalin was questionable. In some of these cases the stains were unsatisfactory, and material was not available for special stains. In 4 cases (6.2 per cent) hyalin was recorded as absent.

Fatty Infiltration.—Roughly, about three fourths of the livers in our series were fatty, and no doubt the increased fat content accounted for much of the increase in hepatic weight. Practically no fat was present

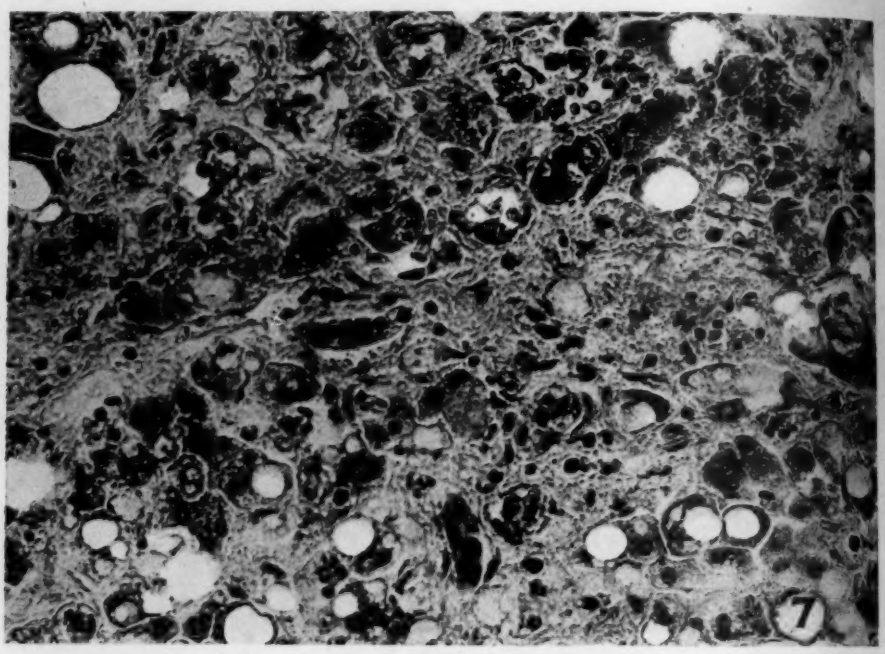

Fig. 7.—The patient was a Caucasian woman aged 56 years. She had chronic alcoholism. The liver weighed 4,400 Gm. The photomicrograph (high power) shows many necrotic liver cells, most of which contain lumpy masses of dark-staining "hyalin." There is more or less new connective tissue, and fibroblasts may be seen growing in among the dead liver cells. The paler areas are edematous. Some of the infiltrating cells are polymorphonuclears. Methylene blue-eosin; × 335.

in the sections of liver in 5 cases, or 7.4 per cent; a small amount was seen in 17 cases, or 25 per cent, and a moderate amount in 15 cases, or 22 per cent; 17 livers (25 per cent) showed a marked fat content; while 14, or 20.6 per cent, were extremely fatty. Roughly, about 50 per cent of the livers contained a large amount of fat.

Damage to the liver cells by phosphorus, alcohol, bacterial poisons, starvation, diabetes and common wasting diseases, such as tuberculosis and malignant tumors, causes accumulation of fat in the liver. Observations at the autopsy table provide ample proof of this. Furthermore, the effects of alcohol and of starvation in producing fatty changes in the liver have been proved experimentally by a number of investigators —in the case of alcohol by Ruge,[13] Friedenwald [14] and Fahr [15] and in the case of starvation by Rosenfeld,[24] Mottram [25] and Dible.[26]

COMMENT

Analysis of the clinical data relative to possible etiologic agents in the 68 cases reviewed by us shows that chronic alcoholism was the factor common to the greater number of patients. We have found no report of a large group of cases showing so high an incidence of chronic alcoholism as in the present series (80 to 90 per cent). Evans and Gray stated that the incidence of cirrhosis in the Los Angeles County Hospital following repeal of the eighteenth amendment increased to three times that of the prohibition period. Their cases cover the prohibition years and the period following repeal up to May 1937. In spite of the decided rise after 1932, the total incidence of alcoholism was only 25 per cent. Boles and Clark [2] reported an incidence of 35 per cent. Mortality statistics for the registration area of the United States (quoted by Rowntree [27]) show a drop of 50 per cent in the incidence of cirrhosis in this country during the prohibition era.

These and many other facts which cannot be included here relate alcoholism and cirrhosis so closely that an etiologic relationship must be seriously considered even though it is not yet proved.

There is a general feeling even among the proponents of the alcohol-cirrhosis relationship that some additional factor is necessary, or that special conditions must be complied with, before alcohol becomes effective in producing cirrhosis.

In our routine autopsies we have had the feeling from time to time that persons having chronic alcoholism who have at the same time a positive Wassermann reaction show more severe hepatitis than those whose hepatic disease is not complicated by syphilis. In the present series, of those livers in which the combination of alcoholism and syphilis was operative, 50 per cent show extreme fibrosis, with broad bands of fibrous tissue not confined to the periportal areas but in their extent and distribution suggestive of hepar lobatum. Of the remaining 58 cases, only

24. Rosenfeld, G.: Ergebn. d. Physiol. **1**:651, 1902.
25. Mottram, V. H.: J. Physiol. **38**:281, 1909.
26. Dible, J. H.: J. Path. & Bact. **35**:451, 1932; **38**:269, 1934.
27. Rowntree, in discussion on Boles and Clark.[2]

20 per cent (in all of which the Wassermann reaction was negative or not recorded) exhibit such extensive fibrosis.

Jaundice was present in 50 per cent of our patients. Omitting the 7 who had terminal bronchopneumonia, we find that 10 patients had acute infections. Twenty-four patients showing clinical jaundice are recorded as having moderate to severe necrosis of the liver cells. In the latter group the condition of the liver may be considered quite definitely the result of the toxic action of alcohol. In 6 instances necrosis was called marked to severe (+ + + to + + + +) on histologic grounds, but clinical jaundice was not recorded. Ascites was found in the same percentage (60.3) in our group as reported by Evans and Gray [18] for the cases of chronic cirrhosis. Fatal hemorrhage from ruptured esophageal varices occurred in 13.9 per cent of their cases and in 20 per cent of ours.

Enlargement of the liver was the most striking anatomic finding in our series. The average weight was 2,760 Gm., which is approximately double the weight of the average hobnail liver. Fibrous tissue is usually abundant in the liver in the cases of subacute cirrhosis but is less mature than in the cases of chronic cirrhosis. Fibroblasts are evident, especially about necrotic liver cells.

A large infiltrate of fat was found in about 50 per cent of the livers in our series. Another 20 per cent were considered moderately fatty.

Connor [20] recently reviewed the subject of fatty infiltration of the liver in relation to alcoholism and cirrhosis. He cited adequate authority for the statement that poisons such as ether, chloroform, carbon tetrachloride and alcohol interfere with carbohydrate metabolism and so with the proper oxidation of fats. His excellent report should be consulted for a more detailed discussion of fatty infiltration of the liver.

That dietary deficiency plays a prominent role in chronic alcoholism and in alcoholic cirrhosis has been emphasized recently by Romano.[28] Of 131 patients with alcoholism studied, 77, or 58 per cent, presented some degree of neuritis, and 61, or 79 per cent, of those showing neuritis had a history of inadequate food intake previous to admission. Sixty-one per cent showed partial improvement and 32 per cent showed complete recovery on specific vitamin therapy.

Patek [29] also studied the matter of dietary deficiency in patients with alcoholism. In 9 of 13 patients the caloric intake was very low. On a diet high in calories plus specific vitamin therapy 10 patients who survived showed decided improvement.

Dr. W. L. Adams, one of the medical house officers of the Los Angeles County Hospital, assures us that a diet high in calories plus high vitamin therapy causes rapid decrease in the size of the liver and relief of

28. Romano, J.: Am. J. M. Sc. **194**:645, 1937.
29. Patek, A. J., Jr.: Proc. Soc. Exper. Biol. & Med. **37**:329, 1937.

symptoms in patients suffering from subacute cirrhosis. The diagnosis in these cases has been definitely confirmed by peritoneoscopic examination and biopsy of the liver. All of the patients have chronic alcoholism. A person who drinks a pint or more of whisky per day must find it difficult to assimulate an adequate amount of food. Since, according to Sollmann,[30] 1 cc. of whisky produces 4 calories of energy, a pint of whisky (50 per cent) would provide approximately 2,000 calories of energy daily. Besides the increase in actual calories, there is likely to be loss of appetite due to gastritis, disturbance of liver function, vitamin B deficiency and other abnormal conditions. Furthermore, the periodic drunkard, who goes on a prolonged debauch, must be for days at a time inadequately nourished or actually in a fasting state. It is common knowledge that a liver so thoroughly depleted of glycogen is vastly more susceptible to damage than one adequately protected by a store of glycogen. It is under these conditions that repeated large doses of alcohol are likely to prove damaging. Not only does fat tend to increase markedly in such livers as a result of the interference with carbohydrate metabolism and with oxidation of fats, but marked anoxemia develops in the liver and the body as a whole, according to Connor.[20]

Corroborative of the foregoing observations, the recent report of Von Glahn and his co-workers[12] is interesting. They found that a diet high in carbohydrate afforded their rabbits marked protection against developing cirrhosis. A group of 26 rabbits received daily amounts of arsenates ranging from 1.86 to 2.4 mg. on a diet of white bread and uncooked peeled white potatoes. Only 2 animals showed cirrhosis, which was of a mild degree, while 24, or 91 per cent, had no increase of hepatic connective tissue. By feeding carbohydrate-poor diets, these workers, using copper, lead and sodium arsenates, had obtained cirrhosis in more than 90 per cent of their animals. It appears that a diet rich in carbohydrates protects the liver from the injurious effect of arsenates when these are given in small doses.

Bollman and Mann[31] cited experiments showing variations in the susceptibility of fatty livers of dogs to alcohol when the glycogen content of the livers was greatly reduced. With feeding of a fat diet, the fat content of the liver by the fourth week had risen to 40 per cent. The glycogen content decreased at the same time to 0.2 to 0.3 per cent. Alcohol of 95 per cent strength fed in doses equivalent to 1.5 cc. per kilogram of body weight to dogs in the aforementioned condition caused coma and intoxication lasting one to two hours. In animals with 50 per cent fat and 0.1 per cent glycogen in their livers a slightly increased dosage (2 cc. per kilogram) usually proved fatal. A dosage of 1.5 cc.

30. Sollmann, T.: Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1932, p. 706.

31. Bollman, J. L., and Mann, F. C.: Am. J. Physiol. **116**:214, 1936.

of 95 per cent alcohol per kilogram in dogs with normal livers caused them to become only momentarily intoxicated. A change from a fat to a carbohydrate diet restored the excessively fatty livers to normal within a week.

LeCount and Singer [16] emphasized the serious effects of a reduction in liver glycogen in chronic alcoholism. They reported a number of cases of sudden death in alcoholic persons who had extensive replacement of the liver by fat. The postmortem examinations revealed little else than large fatty livers.

Not all of the livers in our series were fatty—30 per cent contained relatively small amounts of infiltrating fat. Crandall and Ivy,[32] in a recent review on applied physiology of the liver, stated that in hepatic disease the liver requires increased amounts of sugar in the form of dextrose. They give two reasons for this: In the first place, there is a decreased capacity for storage of glycogen; in the second, the diseased liver is incapable of producing sugar from noncarbohydrate sources (lactic acid, amino acids and glycerol) in order to meet the normal requirements of the body. It appears, therefore, that in alcoholic livers in which excessive fat does not accumulate, there is, nevertheless, increased need of abundant sugar because of the decreased capacity for storage of glycogen and the incapacity of these livers to produce glycogen vicariously. Histologically, all of the livers are diseased, even when there is little or no excess of fat. Connor [20] believes the fatty condition of the liver to be the earliest stage in the development of cirrhosis and that later in many cases excess fat disappears as the fat depots are depleted.

Bloomfield [22] stated that after the onset of symptoms cirrhosis often develops rapidly. There is a long period, often one of years, in which the disease is latent and no symptoms relative to the liver are observed. After the advent of symptoms, the patient may survive for only a few months. Eight of his patients lived less than ten months after symptoms developed, and 2 of these lived only one month. The majority lived ten to forty months. Bloomfield's observations explain, in part at least, the paradox of the rapid increase in mortality due to cirrhosis, a disease usually considered exceedingly chronic, following the repeal of the eighteenth amendment. Resumption of heavy drinking may have precipitated many persons with alcoholism into rapidly fatal cirrhosis.

The question may properly arise as to why some patients die during the subacute phase of alcoholic cirrhosis. In this connection the following observations appear to be important:

(*a*) About 25 per cent of the patients died of acute complicating infections, due largely, no doubt, to marked lowering of their resistance by chronic alcoholism.

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32. Crandall, L. A., and Ivy, A. C.: Surgery **3**:815, 1938.

(*b*) Twenty per cent showed direct effects of alcoholism plus dietary deficiency—half of these had pellagra or peripheral neuritis; in the remaining half either an alcoholic psychosis or delirium tremens developed. Two additional patients had both delirium tremens and pellagra.

(*c*) Hepatic insufficiency is probably an important factor, since 50 per cent of the patients were jaundiced, and 14 per cent showed hepatic necrosis as a cause of death at the postmortem examination. All of the latter were jaundiced.

(*d*) Twenty per cent in our series died of gastric hemorrhage as against 13.9 per cent in the cases studied by Evans and Gray. Therefore portal hypertension appears to be an important cause of death in subacute as in chronic cirrhosis.

SUMMARY AND CONCLUSIONS

A study was made of 68 cases of subacute or progressive alcoholic cirrhosis. The cases were selected from among 12,000 in which autopsies were performed at the Los Angeles County Hospital during the period from 1931 to 1938. They were selected on the basis of liver weights (2,000 Gm. or over) and the presence of hepatic necrosis, portal cirrhosis showing active proliferations of connective tissue, and so-called "alcoholic" hyalin.

Polymorphonuclear leukocytes as well as lymphocytes infiltrated the fibrous tissue. The average weight of the 68 livers was 2,760 Gm. Fifteen weighed between 3,000 and 4,000 Gm.; 6 weighed between 4,000 and 5,000 Gm.

At least 80 per cent of the patients had chronic alcoholism. Only 1 of the 68 patients denied having used alcohol. Jaundice was present in 50 per cent of our patients. In 24 instances the icteric index was 50 units or higher. Approximately 50 per cent of the livers contained excessive amounts of fat. Fatty infiltration was considered moderate in 20 per cent and slight in 30 per cent. Syphilis complicating alcoholic cirrhosis appears to produce a more profound fibrosis than is usually seen in the latter condition alone.

Alcoholism was the outstanding, most common clinical factor in this group of cases. Since the group was selected on anatomic grounds, it appears that the relationship is of real importance. The patient with chronic alcoholism suffers from low intake of carbohydrate, greatly diminished storage of glycogen, fatty replacement of the liver and deficient intake of vitamins. These conditions render the liver especially vulnerable, so that continued abuse of alcohol is followed by necrosis of liver cells and fibrosis, which in the susceptible patient after years results in cirrhosis.

We believe that in the majority of cases the enlargement and fatty infiltration of the liver constitute the first development, that this passes

imperceptibly into the subacute phase of cirrhosis, to be followed later, if the patient survives long enough, by the appearance of the small hobnail liver. A small percentage of the patients die during the subacute stage as a result of complicating infections, dietary deficiency diseases, hepatic insufficiency, portal hypertension, alcoholic psychoses and other disorders.

We believe the term "alcoholic cirrhosis" has a firm basis in etiology. Much of the confusion regarding this subject has been due to the study of cases of chronic Laënnec type among which the cases of cirrhosis due to alcohol cannot be distinguished readily from cases due to other causes.

THE NORMAL, THE ACROMEGALIC AND THE HYPERPLASTIC NEPHRITIC HUMAN NEPHRON

A FURTHER CONSIDERATION OF THE PLASTIC RECONSTRUCTIONS OF LOUIS A. TURLEY

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Some years ago I was struck by the great beauty of three wax models of the tubules of the human kidney which I found preserved in the collection of the Department of Anatomy, Harvard University Medical School. These models, now over twenty years old, were made by Louis A. Turley, then a graduate student at Harvard University, now professor of pathology in the School of Medicine of the University of Oklahoma. They represent (1) the normal nephron, (2) the glomerulus and proximal convoluted tubule in acromegaly and (3) the hyperplastic nephron in chronic nephritis. Models 1 and 3 formed the basis of Turley's doctoral thesis [1]; in the thesis photographs of the two models and several other illustrations are given. This thesis was not published in its original form. In a subsequent paper [2] Turley discussed his findings for the normal and for the nephritic nephron, without, however, mentioning or giving any reproduction of the models in question. The model of the proximal tubule in acromegaly has never been described, either in the thesis or elsewhere.

These three models,[3] all of them beautifully and painstakingly executed, offer data of great interest and value to investigators of the finer structure of the kidney. The model of the normal nephron represents the only instance, up to the present time, in which the reconstruction of an essentially complete adult mammalian nephron—including the loop of Henle—has ever been successfully accomplished. The model

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From the Department of Anatomy, Harvard Medical School.

1. Turley, L. A.: Studies by Reconstruction of the Compensatory Changes in the Tubules in Chronic Diseases of the Kidney, Thesis, Division of Medical Sciences, Harvard University, 1916. (This thesis is on file in the library of Harvard University.)

2. Turley, L. A.: Ann. Med. **1**:401, 1920.

3. The models are numbered as follows in the model collection of the department of anatomy of Harvard University: normal nephron, no. 201; hyperplastic nephron in chronic nephritis, no. 202; glomerulus and proximal convoluted tubule in acromegaly, no. 203.

of the proximal tubule in acromegaly is likewise unique. The model of the hyperplastic nephron in chronic nephritis antedates by many years the recent model of Oliver and Lund [4] and confirms, and to some extent supplements, their findings and the findings in the maceration studies of Oliver and Luey [5] and Loomis.[6]

Under the circumstances, it has appeared to me eminently desirable that a fairly complete series of illustrations of Turley's models, accompanied by a description of his findings, should be made available to other interested workers. I requested Dr. Turley's permission to carry out such a project, and this permission he freely gave. Furthermore, he has cooperated with me to the fullest extent in supplying necessary additional data which were not given in his thesis or in his subsequent publication. I wish to emphasize that my activity has been confined to the study of the models themselves and to the supervision of the illustrations. Mr. Leo Talbert made the photographs, and Miss Etta Piotti made the line drawings. Dr. Turley's findings—based on the models and supplementary studies—will be given in his own words, taken largely from his thesis.

Turley's reasons for undertaking his study are best explained in the introductory paragraphs of his thesis [1] (pages 1 and 2):

> In the studies that have hitherto been made of the changes in the tubules in chronic diseases of the kidney, investigators have turned their attention to the atrophic and degenerative changes only. In no account of the changes in the kidney tubules has any mention been made of any but those of a retrogressive nature, except that Dr. Councilman in his lectures to his students, and in the protocols of autopsies, speaks of hyperplasia of the tubules in some cases. These studies were undertaken to ascertain whether or not the apparent hyperplasia of some of the tubules was really an hyperplasia and if so, to what extent did hyperplasia, or compensatory change take place. And to this end it was decided that the method of studying serial sections, tracing one tubule throughout its length, and making a wax reconstruction of the tubule was the one that was best suited to show the exact amount of change that had taken place.
>
> But before any exact knowledge could be gained of the changes in the pathological tubule, it was necessary to make a careful study of the normal tubule in the adult kidney. Huber [7] in this country, and Stoerk [8] in Germany have carefully worked out the development of the kidney tubule up to the time of birth and have made excellent models of the tubules in various stages of their development, showing the relative size, shape, and the arrangement of the parts. But just what additional changes may have taken place after birth in the complexity of the convoluted portion of the tubule or in the loop of Henle, the diameter of the

4. Oliver, J., and Lund, E. M.: Arch. Path. **15**:755, 1933.
5. Oliver, J., and Luey, A. S.: Arch. Path. **18**:777, 1934.
6. Loomis, D.: Arch. Path. **22**:435, 1936.
7. Huber, G. C.: Am. J. Anat. (supp.) **4**:1, 1905.
8. Stoerk, O.: Anat. Hefte **23**:283, 1904.

normal tubules, whether or not the diameter was constant for one tubule throughout any one of the anatomical divisions, the height of the epithelium and other points that go to make up an exact knowledge of one of these structures has not, so far as the author has been able to find out, ever been made. Therefore, it was necessary to do considerable work on the normal tubule in order to have a basis for comparison in a consideration of the conditions found in the pathological material studied.

Turley was unfortunately not acquainted at that time with the extensive studies of the normal human kidney which had been published some years previously by Peter.[9] In the course of this work Peter reconstructed his now classic, though incomplete, model of the normal adult human nephron. Turley's and Peter's models and observations admirably supplement each other, and will be discussed at greater length later.

METHOD OF RECONSTRUCTION

All three models were reconstructed from serial sections of paraffin-embedded material, stained with hematoxylin and eosin. The following description of the method employed is taken from Turley's thesis [1] (pages 2 and 3):

Drawings of the tubule in the various sections were made with the aid of the camera lucida. At first some difficulty was met in getting the exact relation of the sections of the tubule as it appeared in the various sections, and a number of means were tried to obtain this exact relation. The common method of students of embryology, that of using the outline of the dorsum of the embryo as a guide, was impossible for the reason that the capsule of the kidney is not itself constant on either surface, in the mounted specimen. Ritzer lines were tried and these were found to be, if anything, less reliable than the capsule of the kidney for the reason that in the hands of the author it was impossible to get the sections mounted without distorting the Ritzer lines. Finally the plan to use other structures in the kidney as guides was hit upon and by taking several at a time it was found that the position of any tubule could be maintained through as many sections as it might pass. For this purpose the structures used were glomeruli, blood vessels, and the collecting tubules. And by taking two glomeruli at a time, a collecting tubule and one of the larger vessels it was not difficult to find and maintain the relation of the various sections of any tubule in passing from section to section.

The magnification that was found best suited to this work was two hundred diameters. If a larger magnification were used it would make the model too large and cumbersome, and if a lower magnification were used it would both add to the difficulty of following the tubule and would make the model so delicate that the reconstruction of the entire system into one model would be next to impossible. Therefore all drawings were made with a magnification of two hundred diameters and the wax plates for the reconstructions were made two hundred times the thickness of the sections of the kidney from which the drawings were made.

9. Peter, K.: Die Nierenkanälchen des Menschen und einiger Säugetiere, in Untersuchungen über Bau und Entwicklung der Niere, Jena, Gustav Fischer, 1909, no. 1, p. 1.

The wax plates were made of bees' wax by the method of pouring an accurately weighed amount of melted wax on hot water in a vat of exact dimensions. After cooling, these plates were measured with a micrometer to be sure that they were of the required thickness and no plate was used that was under or over the necessary thickness.

THE NORMAL NEPHRON

Material.—For this purpose I was fortunate enough to find a kidney, which, although it was a little under the normal weight, was nevertheless the site of so few pathological changes that the "brush like inner border" of the epithelium of the tubules was still preserved.[10] Material from this kidney was cut into a series of three hundred sections seven microns thick and mounted in order . . .

This series of sections was studied carefully to find as near as possible an average tubular system. One was finally selected about midway between the capsule and the arcuate vessels, and one from which the tubule left the glomerulus on the side toward the pelvis of the kidney which may be said to be the traditional point of departure of the tubule from the glomerulus, although it was found that the tubule may leave the glomerulus at any point even directly toward the capsule of the kidney irrespective of the position of the system in the cortex. [Thesis,[1] page 2.]

Observations.—By methods outlined above a normal tubule was studied and reconstructed and the results compared with serial drawings of other tubules to ascertain how nearly the reconstructed tubule represented an average tubule, and these facts were used as a basis of conclusions in regard to conditions found in the pathological material studied. A description of a normal kidney tubule, as found by the author, is as follows:

The tubule, from whatever angle it leaves the glomerulus, soon passes toward the capsule, following a tortuous course and continues to bend and turn on itself until it is some distance from the glomerulus. It then turns toward the glomerulus in a more direct course and passes the glomerulus in the descending limb of the loop of Henle. In its course toward the capsule each bend or turn that the tubule makes does not carry it further from the glomerulus, but there may be said to be major and minor turns. That is, the turns lead away from and then toward the glomerulus, and then away again, so that, for example, turn eleven and turn twenty-five are both next to the capsule of Bowman and the turns between eleven and twenty-five are farther away from the glomerulus than either of the two mentioned. It would seem that at some stage in the development of the tubule there were no turns between what is now turns eleven and twenty-five but that the tubule had arched above the glomerulus as a simple bend, and that later the system had become more complex and that the newer turns which had arisen as a result of the lengthening of the tubule had carried part of the tubule farther away from the glomerulus than a part that was really more distal. But eventually the tubule reaches a considerable distance from the glomerulus and then turns toward it again in a more direct direction. In this way the average number of turns in the proximal convoluted tubule, to the point where it again reached the level of the glomerulus on its way to the loop of Henle is forty.

The loop of Henle descends in as nearly a direct direction as the other structures in the vicinity will permit, with the exception that it will sometimes, in some

10. The kidney material for the reconstruction was taken in the course of autopsy no. 15-46 at the Peter Bent Brigham Hospital.

tubules, turn almost at right angles across a cortical ray and turn as sharply again toward the medulla, until it reaches the arcuate vessels. From these structures to the return in the loop it follows a more zigzag course. The thin part of the tubule is comparatively short. The turn is abrupt and the ascending arm of the loop follows a similar, and in general a parallel course to the descending limb of the loop. But it was found that it is not at all uncommon, especially in those tubules that pass below the arcuate vessels, for the ascending limb to have an "S" shaped bend in the medulla before passing the arcuate vessels on their way back to the glomerulus. The ascending limb follows, in general, a more direct course than the descending limb, and in every case passes the glomerulus near the afferent artery. So regular is this that anyone can be sure that he has the ascending limb of the loop of the tubule to any glomerulus by finding the afferent artery to the glomerulus and taking the ascending tubule found there without following out the whole system.

The distal tubule makes few turns, eleven in the system modeled, until it arches to join the collecting tubule.

The shape and diameter of any tubule is not constant for all parts of the system, or even the proximal convoluted part. The shape of the tubule will vary with the pressure of the other turns of itself, or with other structures. The diameter of the tubule in this part is in general greater near the glomerulus, and remains fairly constant for a considerable distance, then there is some reduction in the diameter which, although it is gradual, takes place in a comparatively short space. This reduced diameter is then constant and continues into the descending arm.

In the descending arm there is a gradual reduction in the diameter of the tubule until it reaches a somewhat smaller size which it maintains until it goes over into the thin part of the arm.

The diameter of the ascending arm is constant, or nearly so, throughout its length. That is, there is no region in which the diameter is larger or smaller in general, although it may vary from place to place.

The diameter and shape of the distal convoluted tubule is quite variable, but in general it is greater as it approaches the junctional part, when it again is reduced in diameter to a slight degree.

The measurements of the various parts are as follows: The diameter of the proximal convoluted tubule averages 60 microns to the basement membrane on either side and it varies between 75 and 45 microns; the upper part of the descending arm is 50 microns and the reduced diameter is 45 microns in the lower part; the average diameter of the ascending arm is 37.5 microns; and the distal convoluted varies between 40 and 50 microns.

As the tubule leaves the glomerulus the epithelium changes suddenly from a simple squamous to a high cuboidal, or glandular cuboidal form. The height of this epithelium is 17.5 microns on an average and the free ends of the cells are all on a level so that the lumen of the tubule is sharply defined. The height of the epithelium remains constant throughout the proximal convoluted tubule. The height of the epithelium in the descending arm is 15 microns in the upper part and is reduced very little until the thin part of the arm is reached. At the distal end of the thin part, the epithelium takes on the character of the ascending arm of the loop, so that structurally and functionally the distal part of the system may be said to begin at the distal end of the thin part of the loop of Henle.

From the figures given above it can easily be calculated what the square area of the epithelium in any part of the tubule is. Also what is the perimeter of the lumen of the tubule in any part. Thus the area of the epithelium in an average cross section of the proximal convoluted tubule is 2336.565 square microns, and the perimeter of the lumen at the same point is 78.54 microns. [Thesis,[1] pages 4 to 7.]

THE GLOMERULUS AND PROXIMAL CONVOLUTED TUBULE IN ACROMEGALY

As stated, the model of the glomerulus and proximal convoluted tubule in acromegaly has never been described by Turley, either in his thesis or elsewhere. The model was made over twenty years ago, and Dr. Turley no longer has any record of the autopsy number or any complete description of the kidneys as observed at autopsy. In answer to my request he has, however, supplied the following information:

Dr. Councilman asked me to make a model of the glomerulus and proximal portion of the nephron in an attempt to explain a condition which could not be determined by gross or microscopic examination of the kidney. Dr. Councilman's statement was as follows: "Each of these kidneys weighs twice as much as a normal kidney should, but there is no evidence either grossly or microscopically which will explain the increased size." I remember that at the time microscopic examinations of sections of these kidneys did not show any abnormal histologic character, so that the description would be that of a normal glomerulus and tubule. . . . The material came from Dr. Cushing's clinic for the study of pituitary disturbances. . . . My studies showed that the proximal tubule was twice the length, while the diameter was the same as that of the normal. A comparison of this model with a model of the normal tubule will show that the general structure of the acromegalic kidney was normal, but that the tubule was twice the length of the normal, which accounts for the increased size of the mass in the model.

THE HYPERPLASTIC NEPHRON IN CHRONIC NEPHRITIS

Material.—In selecting material for this study, the material at the Peter Bent Brigham Hospital was gone over carefully and all of the material from chronic diseases of the kidney was studied, and from this several cases were selected, the basis of selection being that there was enough in any one piece of tissue to make a series of at least a hundred sections that would show as much as possible of a section from the capsule to the pelvis. From the cases selected one of them was chosen as a type because the tubules functioning at death had not undergone any great degenerative changes so that the character of the epithelium was as near normal as possible.[11]

The combined weight of the kidneys is 195 grams. They are similar, the most conspicuous thing about them being the small size. The capsule strips with some difficulty, tearing off with it small portions of the underlying tissue and revealing a rough granular surface made up of numerous small elevations from .5 mm. to 1.5 mm. in diameter. In some places this rough appearance is less marked and the tissue seems to be replaced by cicatrization. The kidneys are of a

11. The kidney material for the reconstruction was taken in the course of autopsy no. 14-1 at the Peter Bent Brigham Hospital.

pale color, with red lines in the depressions. On section the consistence is found to be somewhat increased, the surface is extremely pale, of a yellowish to purplish grey color, with a few fine red lines and spots in the cortex and the same in the pyramids. The whole surface is of a rather uniform color, the markings are very indistinct, the line between cortex and pyramids being hard to make out in certain places, while in others it is fairly definite. The average thickness of the cortex is 4 mm., average length of pyramids 15 mm. Ureters and seminal vesicle normal.

Section stained for fat shows small amount of fat, sometimes represented in the desquamated epithelium lying in tubules or in the thin attached degenerated epithelium. The hematoxylin and eosin sections show a generalized glomerular nephropathy, every degree of the lesion of the glomeruli represented up to complete destruction. The tissue is well preserved and the character of the lesions is evident. One of the most striking things in the section is the seeming absence of the glomeruli, due to the enormous degree of complete destruction. In certain of them there is a great increase in the covering epithelium with destruction of the vessels. A formation of hyaline connective tissue involves large areas of the organ. The tubules show a number of conditions; in the connective tissue masses, they are represented as very small epithelian masses or have disappeared; in other places the tubules are dilated and the epithelium so atrophic as to resemble pavement epithelium; many tubules show areas of extensive desquamation of such thin cells, and in others there are piled up masses of degenerated epithelium. This cannot be regarded as an artefact on account of the freshness of the autopsy and the care in taking the specimen. There are certain of the glomeruli in which the damage is much slighter and there are areas of tubules with the epithelium but little changed and which undoubtedly represent areas of hyperplasia. So it will be evident that these kidneys represent a chronic diseased condition where there is a compensatory change.

A series of one hundred and eighty-nine sections, 8 microns thick, was made from a piece of one of these kidneys, and it was studied and modeled in the manner and by the same means as described above for the normal kidney, and the following changes were found to have taken place. [Thesis,[1] pages 7 to 9.]

Observations.—The tubule remains the normal diameter for some distance from the glomerulus, then there is a gradual though quite sudden enlargement until the diameter is doubled or even larger in some places. The average diameter of these hyperplastic tubules was found to be 115 microns on an average, and some were found that were 140 microns in diameter. The tubules were greatly lengthened, one having 95, and one 106 turns in the proximal convoluted part to the point where the tubule passed the glomerulus on its way to the loop of Henle. In some of the single sections the diameter of the tubule was even greater, but by following it through the series so that the diameter vertical to the plane of the section was found it proved to be much less, hence the perimeter of the tubule at that point is not greater than at some point where the enlargement is apparently not so great.

It might be suggested that the apparent increase in the length of the tubule was due to the union of two or more tubules after the glomerulus had ceased to function. And it has been suggested by Felix[12] that in the development of the

12. Felix, W.: The Development of the Urinogenital Organs, in Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 752.

kidney such unions do take place, though sufficient evidence of this suggested phenomenon has not been produced. And against such an assumption in the pathological case is the fact that in the group of hyperplastic tubules there is no evidence that any other glomeruli than the ones now present have ever existed. Students of pathology will remember that no matter how atrophied or fibrosed a glomerulus may become its location can always be found. So the conclusion must be drawn that the apparent increase in the length of these tubules is a real increase and represents an hyperplasia of a compensatory nature.

The epithelium of the tubule as it leaves the glomerulus is reduced to a squamous form, and this change extends for a considerable distance along the tubule, to the twelfth turn in some cases studied. Otherwise the epithelium is apparently normal in character. The average height of the epithelium is 17.5 microns, and the free border of the cells is, in general, on a level although apparently it is somewhat ragged. This apparent ragged border is due in most cases to the adherence of a granular deposit in the lumen of the tubule.

By the same calculations as were made in the case of the normal tubule, the area of epithelium in any cross section of the tubule is 5085.465 square microns or more than twice that of the normal tubule, and the perimeter of the lumen of the tubule almost four times as great. Add to these facts the greatly increased length of the hyperplastic tubule and we see that there is really an enormous increase in the functioning capacity of one of these tubules over that of the normal tubule.

The most remarkable change was found in the descending arm of the loop of Henle. Instead of running the usual straight course, it was turned on itself in sharp angles in both planes at right angles to its long axis, making in all 79 turns. It was greatly enlarged, the average diameter was nearly as great as that of the hyperplastic convoluted portions, being from 75 to 95 microns, and the epithelium was of the same character in all respects as that of the convoluted portion. And the perimeter of the lumen was as great as the outside perimeter of the epithelium of the normal tubule.

The figures given above are only averages, as the diameter of the tubule at various points was by no means constant either in the convoluted portion or in the loop. There were increases in size at some points that amounted almost to cysts and at other points the tubule was not much above normal. The increase in size at the various points seemed to depend on the pressure of the surrounding tissues. But taking it as a whole the above figures are a fair average of the enlarged condition.

Unfortunately it was not possible, in any of the series of sections that were obtained, to follow the tubule around the turn in the loop or even to find the thin part of the arm for the reason that the material was taken at random at the time of autopsy without any reference to making any use of it but for the common laboratory uses of diagnosis. In one case the specimen did not include all of the tissues from the capsule to the pyramid, and in another the specimen was too thin so that the tubules, running at an angle to the plane of the knife in taking the specimen, did not run the entire depth of the specimen. Therefore, this account does not include an entire tubule, and it must be left until the proper material can be secured before making it complete.

The changes in the ascending arm of the loop were slight in comparison to those that were found in the descending arm. The diameter was somewhat increased, being on an average 50 microns, and it was as constant as the diameter

of the normal ascending arm. The arm was also somewhat bent and turned to follow, in general, the course of the descending arm. The epithelium was of the same character as that of the normal distal convoluted tubule, taking a more dense and uniform stain than that of the normal epithelium of the ascending arm.

The distal convoluted tubule was enlarged, being 70 microns on an average. The number of turns was not increased or but by few more turns than in the normal. The epithelium was the same in character and thickness as the normal but it was in some places in some of the tubules, thrown into folds or rugae.

After completing the study of the tubules in this case, the tubules in other cases were studied by the examination of serial sections and making serial drawings. The same changes as described above could be traced in all of the cases of chronic disease of the kidney that were available. However, the changes were not so great in all cases, and the retrogressive changes in the hyperplastic tubules in some cases were great enough to almost mask the compensatory changes.

By comparison of the normal with the functioning tubules in chronic disease of the kidney the conclusion may be drawn that there is a compensatory change. This change is greatest in the descending arm of the loop of Henle for the reason that it departs the most widely from the normal. The change is that of an increase in the length of the tubule system and an increase in the epithelium at all points, which results in an increase in the diameter of the tubule. [Thesis,[1] pages 9 to 12.]

The thesis contains no histologic description of the glomerulus of the particular hyperplastic nephron which was reconstructed, but Dr. Turley has supplied such a description for inclusion in this report, as follows:

There is a slight increase in the subcapsular space, which contains a small amount of precipitated albuminous material and a few desquamated cells. The lobulation of the glomerular tuft is still apparent. In most of the lobes the intercapillary spaces have been obliterated; in some cases this has been caused by fibrous tissue, and in other cases there is an apparent obliteration due to precipitation of albuminous material similar to that in the subcapsular space. In some of the lobes the capillaries are gorged with red cells. There has been formed a new epithelial capsule around the tuft, which is continuous across the intercapillary loops. In one place, at the tip of the tuft, next to the neck of the tubule, this epithelium seems to be almost of the columnar type; in most of its extent, however, it is formed of cells of a thick, squamous character. In some of the capillaries, especially the main intralobular branches, there is hypertrophy of endothelium, but apparently in no case does it completely close the capillary. There are no histologic reasons apparent why a fairly good supply of blood should not pass through this glomerulus. There are no adhesions between the glomerular tuft and the capsule. The epithelium of the capsule is fairly normal.

The greatest diameter of the glomerulus as measured by Dr. Turley from the original sections is 275 microns from capsule to capsule. As measured from the model, the maximum diameter at right angles to the direction aforementioned is 235 microns, and at right angles to the latter measurement the diameter is 170 microns. Compared with the normal, the glomerulus is obviously considerably enlarged.

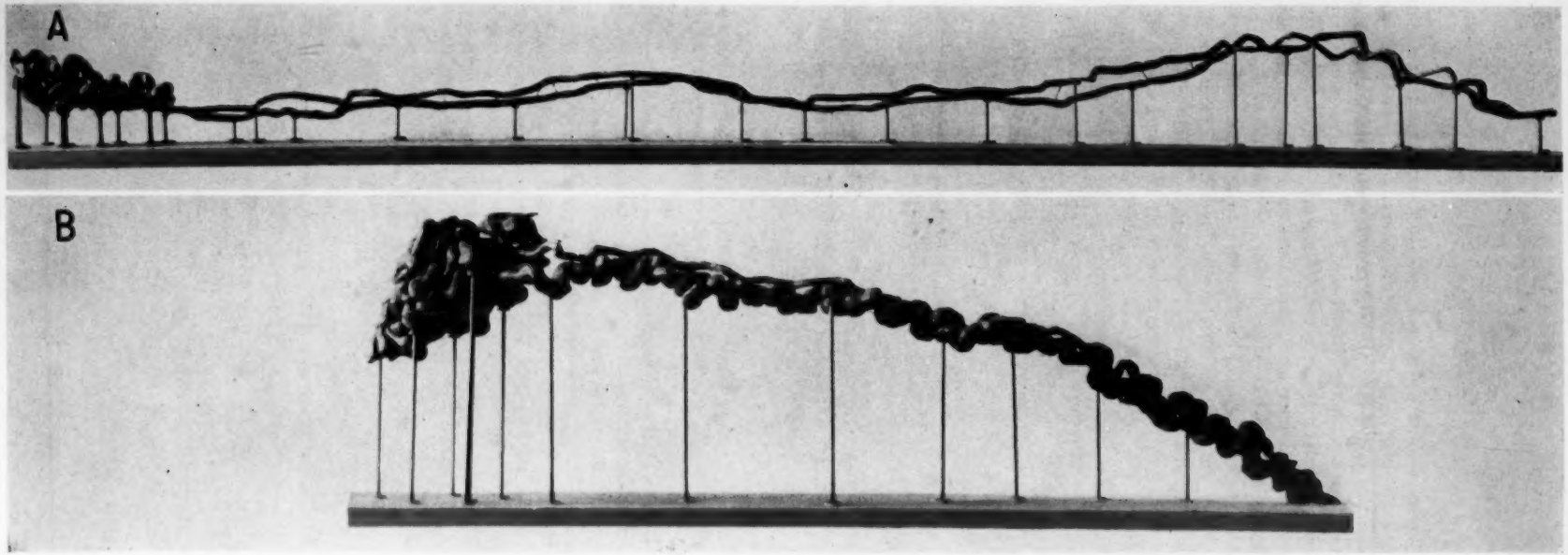


Fig. 1.—*A*, photograph of the model of the normal nephron. It is approximately one eighth of the actual size of the model. *B*, photograph of the model of the hyperplastic nephron in chronic nephritis. It is approximately one eighth of the actual size of the model.

A.
B
C

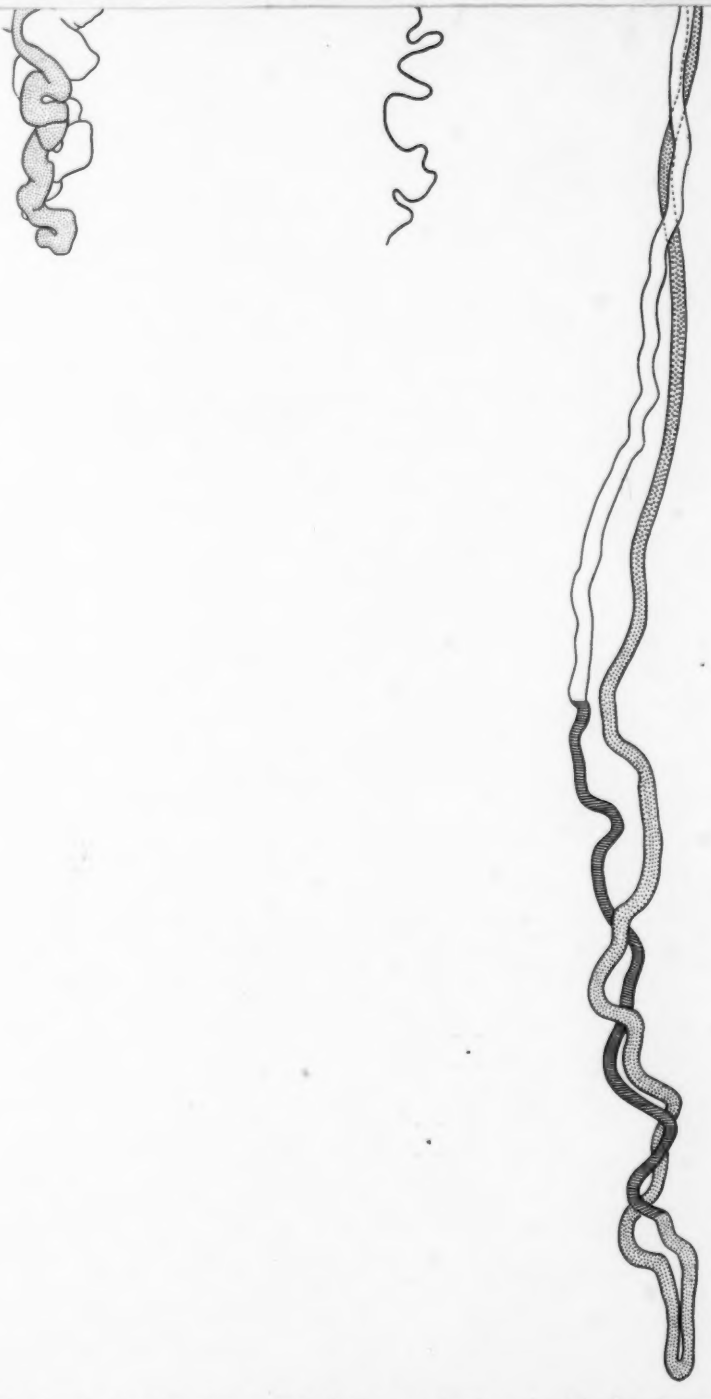
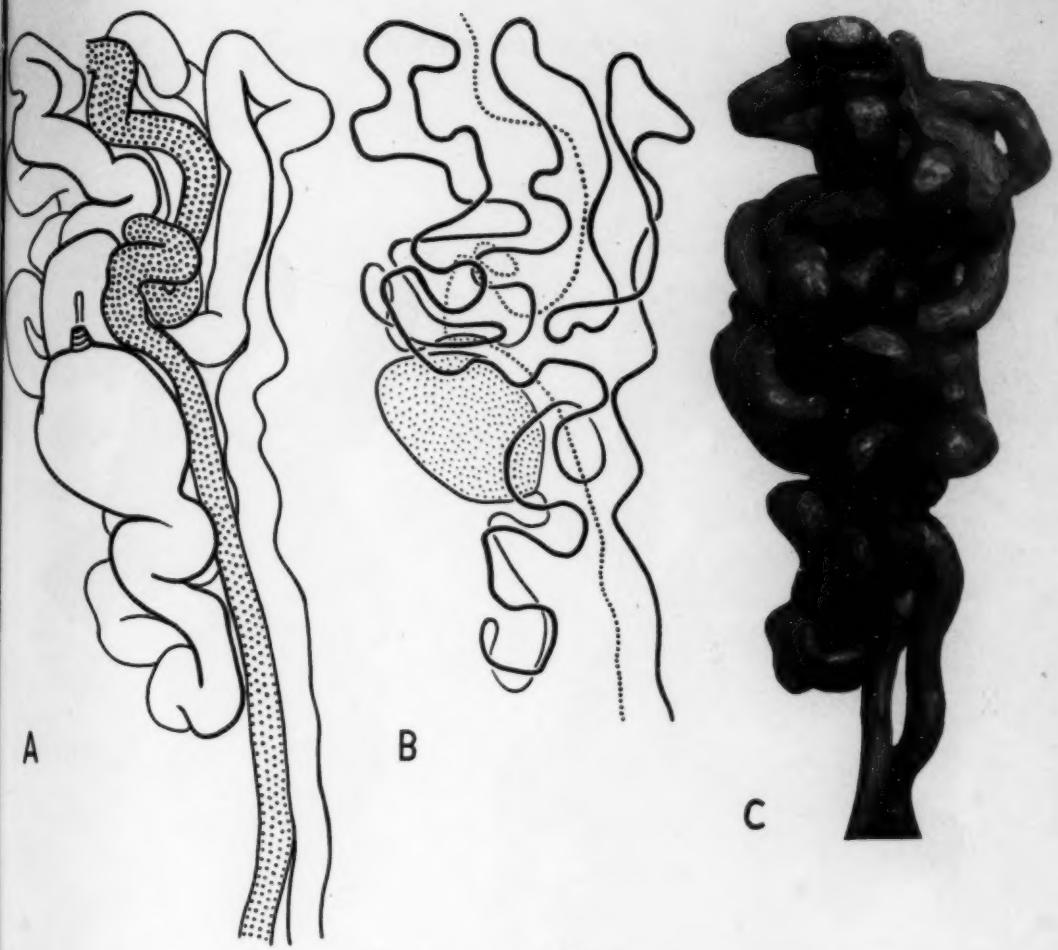


Fig. 2.—*A*, drawing of the model of the hyperplastic nephron in chronic nephritis, looking vertically down on the model. The glomerulus and proximal tubule (pars convoluta and pars recta) are represented by simple lines. The distal tubule is dotted, and the cut surface of the distal tubule (which is located above and to the right of the glomerulus) is cross lined. × 50.

B, a "wire" diagram, analyzing the course of the markedly irregular pars recta of the proximal tubule in the hyperplastic nephron in chronic nephritis. This drawing is oriented the same as *A*. × 50.

C, drawing of the model of the normal nephron as viewed at an angle of about 60 degrees to the horizontal. The glomerulus (to the left of and below the main mass of the convoluted portion) and the proximal tubule (pars convoluta and pars recta) are represented with simple lines. The thin segment is cross lined, and the distal tubule is dotted. In the original model the glomerulus and entire proximal tubule are colored green, the thin segment yellow and the entire distal tubule brown; the point of entrance of the afferent vessel is shown as a small projection, colored red. × 50.



EXPLANATION OF FIGURE 3

A, Drawing of the inferior aspect of the convoluted portions of the normal nephron to show the first portion of the proximal convoluted tubule as it leaves the glomerulus and the course of the distal convoluted tubule (dotted). The short projection (cross lined) at the superior pole of the glomerulus represents the point of entrance of the afferent vessel. This view of the model was obtained by the use of a mirror, and is at somewhat of an angle from the horizontal plane. × 100.

B, a "wire" diagram of the convoluted portions of the normal nephron, analyzing the course of the proximal (solid line) and distal (dotted line) convoluted tubules. The oval dotted area to the left represents the glomerulus. The diagram is oriented as in *C* for comparison. Where one portion of the proximal convoluted tubule passes under another portion, this is indicated by a break in the black line. The distal convoluted tubule is all located on the inferior aspect of the model (see *A*) and at no point intertwines with the convolutions of the proximal tubule. × 100.

C, photograph of the convoluted portion of the normal nephron. The glomerulus is located to the left of the center, and the point of entrance of the afferent vessel is shown as a small projection from the superior pole of the glomerulus. At the bottom of the picture the beginning of the pars recta of the proximal tubule is seen to the right, and the upper portion of the pars recta of the distal tubule is seen to the left. Except for these short portions of the descending and ascending limbs and of the glomerulus, the entire tubular mass illustrated belongs to the proximal convoluted tubule. The photograph shows the view obtained by looking directly down on the model, and *B* is similarly oriented for comparison. × 100.

Fig. 4.—*A*, photograph of the superior aspect of the model of the glomerulus (seen at the inferior pole of the main mass) and the proximal convoluted tubule in acromegaly. The upper portion of the pars recta of the proximal tubule is shown below and to the right. × 100.

B, photograph of the model of the glomerulus and proximal convoluted tubule in acromegaly, viewed from the side (at right angles to *A*). × 100.

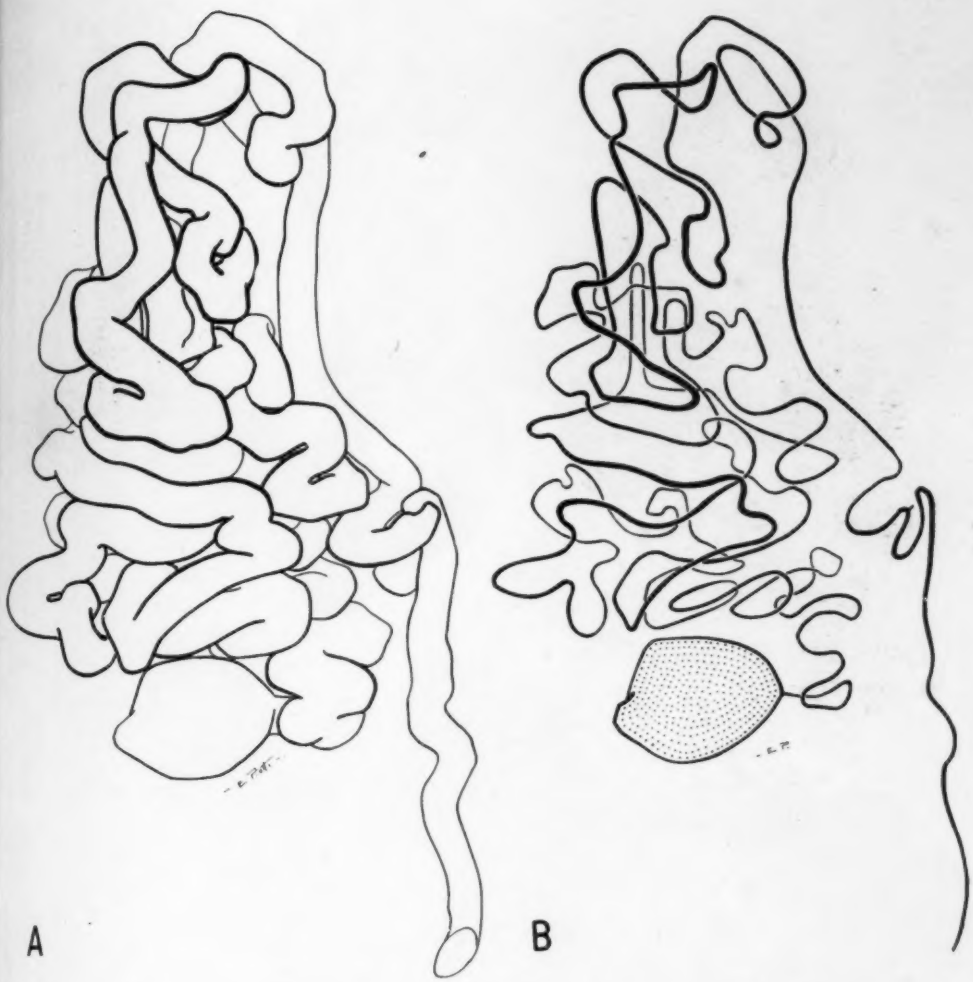


Fig. 5.—*A*, drawing of the model of the glomerulus and proximal convoluted tubule in acromegaly, oriented as in figure 4 *A*. × 100.

B, a "wire" drawing of the proximal convoluted tubule in acromegaly, analyzing the course of the convolutions. The figure is oriented as in figures 4 *A* and 5 *A*. The oval dotted area represents the glomerulus. Where one portion of the proximal convoluted tubule passes under another portion, this is indicated by a break in the black line. The linear representation of the pars convoluta shows a short projection near the beginning of the pars recta (to the right, below the center). This represents a small diverticulum of the tubule at this point; this diverticulum can be seen in figure 4 *A* on careful examination, and it is illustrated in *A* in the present figure. × 100.

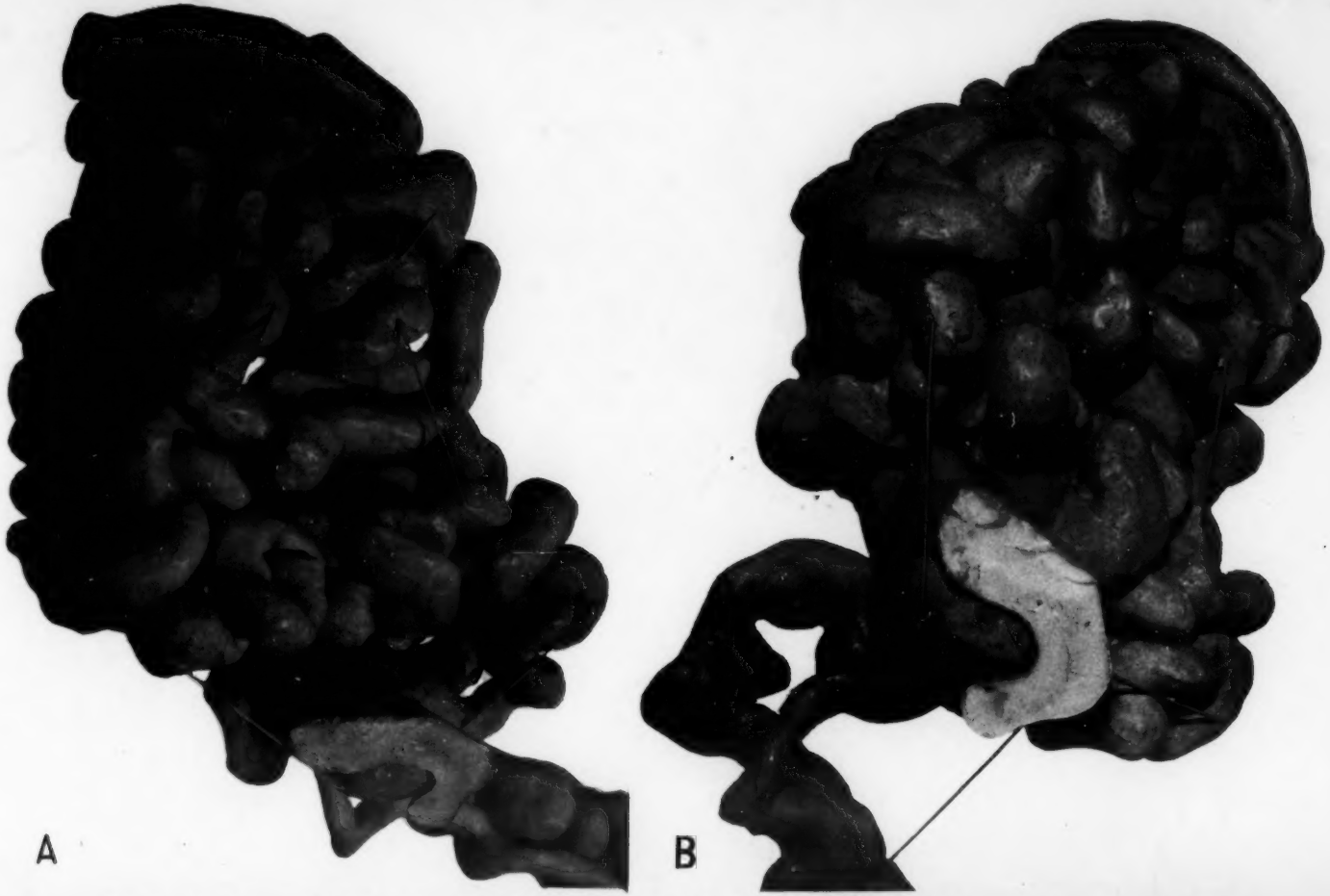


Fig. 6.—*A*, photograph of the enlarged proximal convoluted tubule in the model of the hyperplastic nephron in chronic nephritis. This is a side view, taken at an angle of about 45 degrees. It is a view of the side opposite that shown in figure 1 *B*. The entire mass shown is the proximal tubule with the exception of a short stretch of the distal tubule (at the lower right hand corner; compare *B*). The glomerulus and its urinary pole can be seen behind and to the right of the cut surface of the distal tubule. × 100. *B*, photograph of the upper portion of the model of the hyperplastic nephron in chronic nephritis, looking directly down on the model. The irregular light gray area represents the cut surface of the distal tubule (compare figures 2 *A* and 7 *B*, which are oriented in the same way). The glomerulus is located to the left of, and behind, this cut surface. In the lower left hand corner a short stretch of the distal tubule can be seen overlying the proximal

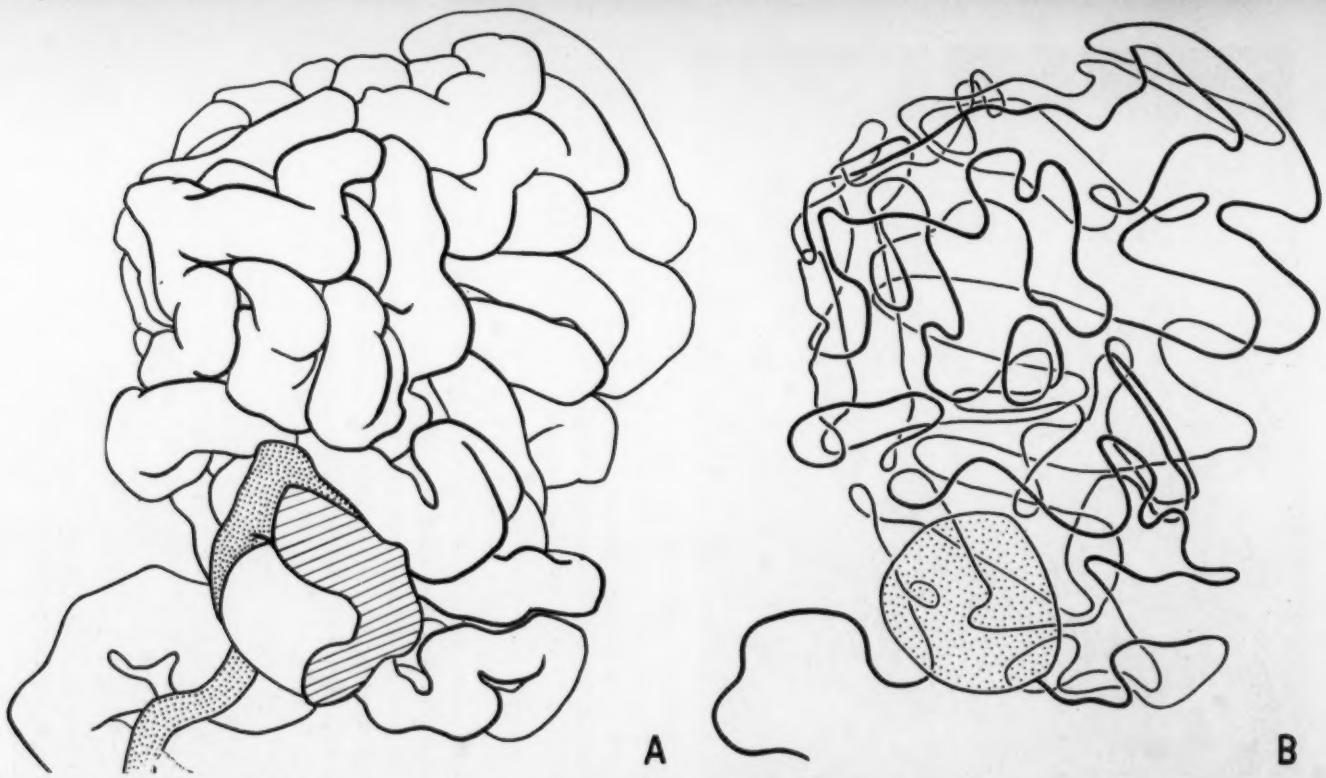


Fig. 7.—*A*, drawing of the convoluted portion of the hyperplastic nephron in chronic nephritis. This is the upper portion of figure 2 *A*, reproduced at larger magnification for direct comparison with *B*. × 100. *B*, a "wire" diagram of the proximal convoluted tubule in the hyperplastic nephron in chronic nephritis, oriented the same as in *A*. The dotted area represents the glomerulus. Where one portion of the proximal convoluted tubule passes under another portion, this is indicated by a break in the black line. × 100.

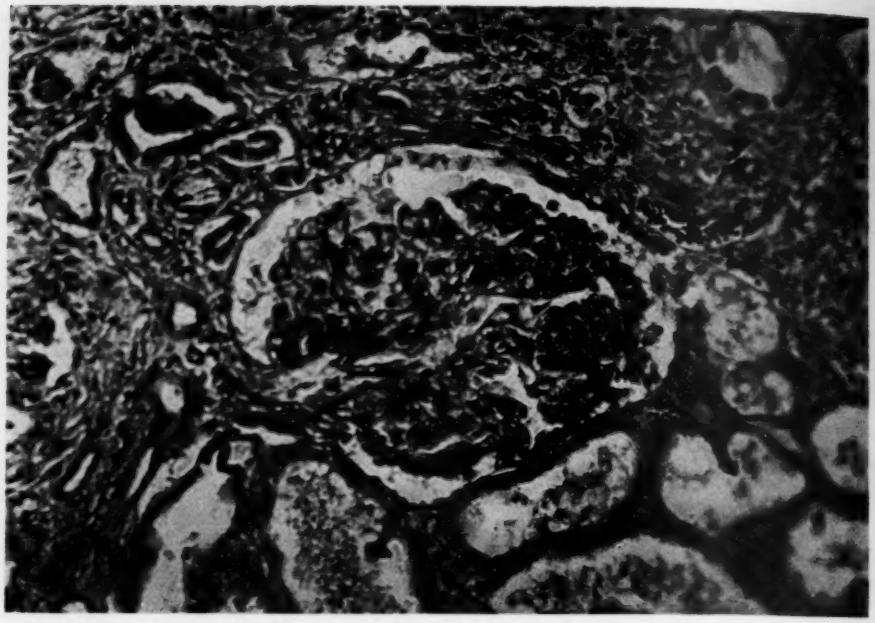


Fig. 8.—Photomicrograph of the glomerulus of the hyperplastic nephron modeled by Turley. The urinary pole is to the right, and the flattened character of the epithelium of the first portion of the proximal tubule is well shown. The sectioned tubules beneath and to the right of the glomerulus are portions of the hyperplastic proximal tubule of the same nephron. The photograph was supplied by Dr. Turley.

COMMENT

The Method of Reconstruction.—Turley's description of his method of reconstruction has been quoted in the foregoing part of this article in detail because of Peter's [9] statements concerning the extreme difficulty of reconstructing adult mammalian urinary tubules. For a discussion of the use of orientation lines (Ritzer lines, etc.) in reconstruction, it is sufficient here to refer to the well known paper of Born and Peter.[13] In Peter's modeling of the adult human nephron (see comment later) the serial sections were provided with such base or orientation lines, supplied by coating one surface of the paraffin block with "nubian blacking." These lines he considered indispensable, stating that in his opinion it is impossible to make an accurate reconstruction of such a complicated tubule without them. Nevertheless, from the recent experiences of Oliver and Lund,[4] from my own experience in modeling the nephrons of lower vertebrates [14] and from the

13. Born, G., and Peter, K.: Ztschr. f. wissensch. Mikr. **15**:31, 1898.

14. Grafflin, A. L.: Anat. Rec. **68**:287, 1937.

general experience of other workers in modeling various tissues, I am entirely convinced of the adequacy of the method Turley employed, and I believe that his models can be accepted as wholly accurate plastic representations of the nephrons which he studied.

The Normal Nephron.—In addition to Turley's model, only one other extensive plastic reconstruction of the normal adult human nephron has ever been produced. This is the well known model made by Peter,[9] which is less complete than Turley's in that it does not include the loop of Henle, but more complete in that it includes (*a*) the entire junctional tubule and a portion of the collecting duct into which tubule drains, (*b*) the afferent vessel and a portion of the interlobular[15] vessel from which the afferent vessel arises and (*c*) a portion of the efferent vessel. Peter's excellent illustrations should be compared in the original with those given here, since the two models supplement each other so excellently. The present illustrations have for the most part been reproduced at the same magnification as in Peter's article (× 100) to render such a comparison easier and more profitable. At the same time, drawings of the nephritic and normal nephron have been reproduced (fig. 2*A* and *C*) at the same magnification as those of Oliver and Lund (× 50) for purposes of comparison.

A consideration of Turley's model shows that it probably represents a fairly typical "short loop" human nephron. The glomerulus[16] and proximal convoluted tubule of the nephron lay "about midway between the capsule and the arcuate vessels" (see quoted paragraph, page 694); the thin segment is quite short (about 1.5 mm.), and the bend in the loop of Henle occurs in the distal tubule. As Peter[9] demonstrated, "short loop" nephrons are at least seven times as numerous as "long loop" nephrons. The glomeruli of the latter lie deep in the cortex, and the bend in the loop of Henle regularly occurs in the course of the thin segment, which is usually quite long. It is to be emphasized that in an occasional human nephron the thin segment is entirely absent, the proximal tubule continuing directly in the distal tubule.[17] The glomer-

15. This is the usual designation for these vessels. It is in keeping with the concept of a structural unit of the kidney built about the collecting ducts, in the sense of H. F. Traut (The Structural Unit of the Human Kidney, Contrib. Embryol. **15**:103, 1923). W. von Möllendorff (Der Exkretionsapparat, in Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 1, p. 1), on the other hand, sharply disagrees with this usage; he supports instead the concept of a vascular unit of the kidney, built about the so-called interlobular vessels, which he designates "intralobular."

16. The size of the glomerulus as measured from the model is approximately 235 by 163 microns—almost identical with the glomerulus in the model of the acromegalic nephron.

17. Peter, K.: Zum feineren Bau der menschlichen Niere, in Untersuchungen über Bau und Entwicklung der Niere, Jena, Gustav Fischer, 1927, no. 2, p. 449; footnote 9.

uli of such nephrons lie peripherally in the cortex, and the loop is confined to the cortex or extends only a short distance into the medulla.

In both the Peter and the Turley model the ascending limb of the loop of Henle "returns" to apply itself to the glomerulus of the same nephron, lying in close apposition to the vascular pole. This relationship was first shown by Golgi [18] and was confirmed and shown to be invariable—in man and all other mammals investigated—by Hamburger [19] and Peter.[9] The latter investigators emphasized the close relationship of the distal tubule to the vas efferens. That the essential relationship is, rather, to the vas afferens, Turley was apparently the first to appreciate. In his thesis he strongly insisted on this relationship and stated that "anyone can be sure that he has the ascending limb of the loop of the tubule to any glomerulus by finding the afferent artery to the glomerulus and taking the ascending tubule found there without following out the whole system."

This dictum of Turley's has been strongly reenforced by the extensive study of Michailovitch.[20] As is now well known, the epithelium of the distal tubule shows a striking dense accumulation of nuclei—the "macula densa," so named by the late Prof. K. W. Zimmermann—at the point of apposition to the vascular pole of the glomerulus. In a reinvestigation of the problem of the exact relationship of the ascending limb to the glomerulus, Michailovitch made a careful study of the "macula densa" in twelve different species: man, baboon, rhesus monkey, horse, cat, dog, pig, ox, rabbit, guinea pig, mouse and rat. His conclusions may be briefly summarized: In all animals investigated the ascending limb is in direct apposition to the vascular pole of the glomerulus and, more specifically, is intimately attached to the vas afferens near its point of entrance into the glomerulus. That this intimate association with the vas afferens is the important and essential relationship is shown by the fact that one finds here, and only here, the formation of the "macula densa" in the tubular wall. The "macula densa" is developed only on one side of the tubule—the side adjacent to the vas afferens—and is of variable length, with a maximal observed length in man of 66.6 microns. The ascending limb usually crosses the vas afferens at the point of contact but can lie lengthwise along it (observed in the dog and the pig). The close packing of the nuclei was found to be less marked in the cat than in any of the other animals investigated.

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18. Golgi, C.: Rendic. d. r. Accad. d. lincei, Cl. di sc. fis., mat. e nat. **5**:334, 1889.

19. Hamburger, O.: Arch. f. Anat. u. Entwcklngsgesch., 1890, supp., p. 15.

20. Michailovitch, V.: Wie verhält sich der aufsteigende Schenkel der Henle'schen Schleife zum corpusculum renis? Inaug. Dissert., Berne, Switzerland, 1919 (unpublished; consulted in the original in Berne).

Djokic [21] observed the "macula densa" in the bear and confirmed its association with the vas afferens, and Belosavitch [22] made the same observation for the llama. Von Möllendorff,[23] in his recent treatise on the kidney, fully accepts the conclusion of Michailovitch (and so of Turley, though the latter's work was unknown to him) that the essential relationship of the ascending limb is with the vas afferens.

In view of the invariability of this association of the ascending limb with the vascular pole, and in particular with the vas afferens, of the glomerulus of the same nephron, it seems that one need never again experience the difficulties encountered by Oliver and Lund.[4] In describing the technic of making their reconstructions of the atrophic and hypertrophic nephrons in chronic nephritis, they wrote as follows:

> The identification of the distal convolution, including the connecting tubule and the collecting tubule, offered a somewhat more difficult problem. No certain point of departure was available, since it is impossible to trace the tubule through Henle's loop . . . and then back to the region of the glomerulus. Cross-sections of what appeared to be the corresponding distal convolutions were therefore chosen and followed through the drawings. The fifth attempt proved successful, as was shown by the inclusion of the selected tubule within the loops of the proximal convolutions.

In concluding the comment on this aspect of the problem, it is well to point out that an intimate apposition of the future distal tubule to the glomerulus dates from the very beginning of the embryologic development of the nephron and is never lost in the subsequent development of the loop of Henle.

Although it is not specifically stated in his thesis, Dr. Turley has informed me that the model of the normal nephron includes the entire distal convoluted tubule and is interrupted at the point where the latter joins the junctional tubule.

The Glomerulus and Proximal Convoluted Tubule in Acromegaly.—As stated, Turley's model of the glomerulus and proximal convoluted tubule in acromegaly is entirely unique. That the disease is usually characterized by "a general splanchnomegaly of the viscera which is disproportionate to the general enlargement of the body" and that the liver and kidneys are particularly enlarged have been emphasized by Cushing and Davidoff.[24] They gave the average combined weight

21. Djokic, A. M.: Zur Histologie der Bärenniere, Inaug. Dissert., Berne, Switzerland, 1919 (unpublished; consulted in the original in Berne).

22. Belosavitch, N.: Ueber den Bau der Lamaniere, Inaug. Dissert., Berne, Switzerland, 1919 (unpublished; consulted in the original in Berne).

23. von Möllendorff, W.: Der Exkretionsapparat, in Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 1. p. 1.

24. Cushing, H., and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance, Monograph 22, Rockefeller Institute for Medical Research, 1927.

of the kidneys in 25 cases as 576 Gm., with a maximum of 1,170 Gm. They further stated that in their own cases "the huge organs on the whole have been well within histologically normal limits."

It will be recalled that in the case in which Turley made his reconstruction the weight of the kidneys was approximately twice the normal and that no abnormal histologic change was observed. The essential fact contributed by the model is that in the case of acromegaly studied by Turley the pars convoluta of the proximal tubule of the particular nephron reconstructed had undergone a striking increase in length but not in diameter and that the increase in length was roughly proportional to the enlargement of the kidney as a whole (approximately twice normal). The size of the glomerulus as measured from the model is approximately 235 by 160 microns, which is within the normal range. In 2 of 4 cases of acromegaly reported by Cushing and Davidoff, on the other hand, as they definitely stated, the glomeruli were enlarged (those in case I being "large"; those in case III, "distinctly enlarged" —average diameter, 250 microns), and Schultze and Fischer [25] reported a marked enlargement of the glomeruli (diameter, from two to three times normal) in a case of theirs. With respect to the tubules, Cushing and Davidoff stated that "the tubules, particularly the convoluted, are definitely dilated" (their case I) and again that "all the tubules are large, the convoluted average 90 μ in diameter as compared with a normal of 70 μ" (their case III). To my knowledge, no measurements of the length of the renal tubules in cases of acromegaly have ever been reported.

Obviously, a great deal more work must be done in order to clarify the factors underlying the enlargement of the kidney in acromegaly. Turley's model is a distinct contribution but represents, after all, only a single glomerulus and proximal convoluted tubule in a single case. Accurate measurements of large numbers of complete nephrons and of their various subdivisions are clearly desirable; for such a study the maceration technic, supplemented by examination of histologic sections, would be the method of choice.[26]

The Hyperplastic Nephron in Chronic Nephritis.—There is available only one other model of the hyperplastic nephron in chronic nephritis with which Turley's model can be compared, namely, that of Oliver and

25. Schultze, F., and Fischer, B.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**: 607, 1912.

26. The maceration technic has been applied by Peters (Peters, E.: Arch. f. Zellforsch. u. mikr. Anat. **8**:63, 1928) to kidneys showing compensatory hypertrophy after unilateral nephrectomy. The study was carried out on white mice. While there was some increase in glomerular size, the most striking finding was an increase in the length of the proximal tubule; unfortunately, the measurements did not include the remaining segments of the nephron.

Lund.[4] Their model is less complete than Turley's in that it does not include any significant portion of the ascending and descending limbs of Henle's loop, but more complete in that it includes (*a*) the entire distal convoluted tubule, the junctional tubule and a portion of the collecting duct into which the latter drains, (*b*) the afferent vessel and a portion of the interlobular vessel from which the afferent vessel arises, and (*c*) a portion of the efferent vessel. The two models supplement each other well, and the Oliver and Lund illustrations should be carefully compared with those given here. The outstanding feature of the hyperplastic nephron in chronic nephritis is clearly a massive enlargement of the proximal tubule. The remaining segments of the nephron share not at all in this hypertrophy or do so to only a very minor extent. Though the Oliver and Lund model includes only the pars convoluta of the proximal tubule, Oliver and Luey [5] subsequently demonstrated, by maceration studies, that the enlargement involves as well the entire pars recta, which shows a remarkably tortuous course, being folded back and forth on itself. The strikingly altered appearance of the pars recta of the proximal tubule is well shown in Turley's model, although it is to be emphasized that the model is not complete in this respect, i. e., stops short of the transition to the thin segment.

The status of the glomeruli in the two reconstructed hyperplastic nephrons is interesting. The histologic description of the glomerulus in Turley's nephron leaves no doubt that the functional capacity of the glomerulus must have been markedly reduced. In the nephron of Oliver and Lund the glomerulus was definitely increased in size, but "the great majority of the tuft capillaries and the greater part of Bowman's space were obliterated, and the original free surfaces, which must have been of great importance in glomerular activity, were greatly reduced." In other words, from the functional standpoint their hyperplastic nephron was essentially "aglomerular." From the data available, such functionally aglomerular nephrons must be of very frequent occurrence. Furthermore, Oliver and Luey [27] were able to demonstrate the not infrequent occurrence of truly aglomerular nephrons, in which all physical connection with the glomerulus had been lost by a complete interruption of the nephron at some point in the proximal tubule. Yet these functionally aglomerular and truly aglomerular nephrons must be considered, from the morphologic point of view at least, as capable of considerable functional activity.

As is now well known, aglomerular kidneys occur in many species of teleostean fishes, a fact which has been of considerable interest in studies of the physiology of the vertebrate nephron (for a broad state-

27. Oliver, J., and Luey, A. S.: Arch. Path. **19**:1, 1935.

ment of the problem see Marshall [28]). Important for present consideration are the following facts: (1) The naturally occurring aglomerular nephron in the teleost consists solely [29] of a segment provided with a brush border, i. e., the homologue of the proximal tubule of the higher vertebrates; [14] such aglomerular nephrons show a marked capacity for tubular excretion.[30] (2) In glomerular teleosts in which the nephron exhibits only the proximal tubule, the latter segment likewise shows considerable tubular excretion, and when such nephrons are rendered functionally aglomerular by the injection of repeated large doses of phlorhizin the tubular excretory capacity of the proximal tubule can be quite marked.[30]

The interest of these facts in connection with the findings of Oliver and his associates and of Turley in human nephritis is obvious. In the hyperplastic nephrons which they have studied and which may be functionally or truly aglomerular, it is only the proximal tubule which shows massive enlargement, the remaining segments of the nephron remaining essentially normal. The proximal tubule is the only subdivision invariably present in the vertebrate nephron, and it appears to be the fundamental segment of the renal tubule. In the lower vertebrates the excretory capacity of the proximal tubule—whether a glomerulus is present or not—has been adequately demonstrated. In man, on the other hand, tubular excretion—under normal conditions—apparently plays a very minor role in the formation of urine.[31] Since in advanced chronic nephritis the burden of renal function is apparently borne in large measure by the hyperplastic nephrons, since massive enlargement is exhibited only by the proximal tubules and since these hyperplastic nephrons may be functionally or truly aglomerular, it appears reasonable to assume that such hyperplastic nephrons are the site of marked tubular excretion and that this tubular excretion—primarily at least—is taking place in the enormously hyperplastic proximal tubule. The implication is that the proximal tubule, primarily reabsorptive in man under normal conditions, is able, under certain pathologic conditions, to develop in marked degree the capacity for tubular excretion which characterizes this segment in lower vertebrates. Important in this connection is the following general conclusion of Marshall: [28] "In the human kidney, where filtration-reabsorption appears under ordinary conditions to play

28. Marshall, E. K., Jr.: Physiol. Rev. **14**:133, 1934.

29. There is likewise present a short junctional tubule such as characterizes all vertebrate nephrons; this junctional tubule is usually regarded merely as a conduit and will be disregarded in the present discussion.

30. Marshall, E. K., Jr., and Grafflin, A. L.: J. Cell. & Comp. Physiol. **1**:161, 1932.

31. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937.

a predominant role for the normal urinary constituents, it is possible that under certain pathological conditions the more primitive secretory process in the tubule may be of major importance."

MacNider,[32] in his studies of experimental chronic nephritis from uranium nitrate in dogs, pointed out that in areas of the kidney exhibiting complete obliteration of the glomeruli "a modified type of (proximal) convoluted tubule epithelium has been preserved"; he went on to state that "such areas resemble the normal structure first described by Marshall[33] for the aglomerular toadfish, Opsanus tau." On the basis of his observations MacNider suggested the possibility "that an organ, the seat of processes of degeneration followed by repair, may as a result of the latter process revert back to a type of structure normal for a remote ancestral form."

The occurrence and probable significance of the aglomerular nephrons in human chronic nephritis were extensively discussed by Oliver and Luey,[27] whose treatment of the problem should be consulted. These authors and later Loomis[6] likewise discussed in detail the problems associated with the maintenance of an adequate blood supply to the diseased kidney. In the latter connection I should like to call attention here to the recent and very important contribution of Spanner,[34] who was able to demonstrate the occurrence of arteriovenous anastomoses in considerable numbers in the normal human kidney.

Some years ago I was faced with the paradox of a kidney which exhibited numerous glomerular structures anatomically, yet behaved functionally as a completely aglomerular organ.[35] This observation was made in an old specimen of Myoxocephalus scorpius (a marine teleost), and it became necessary to attempt to reconcile the anatomic with the physiologic observations, particularly since younger specimens of the same species gave some evidence of glomerular function, and since the kidney of a closely related species, Myoxocephalus octodecimspinosus, regularly showed marked glomerular function.[36] Histologic study of the kidney in a series of specimens of M. scorpius, varying in weight from 85 to 1,006 Gm., satisfactorily explained the paradox in the very old specimen and led to the following conclusions:

The glomeruli have been rendered incompetent by degenerative changes affecting both the vascular tufts and the neck segments, so that it is practically impossible to find a single glomerulus which on anatomical grounds can be considered functional. In young fish of the same species there can be found adequate anatomical

32. MacNider, W. deB.: Proc. Soc. Exper. Biol. & Med. **31**:293, 1933.

33. Marshall, E. K., Jr.: Bull. Johns Hopkins Hosp. **45**:95, 1929.

34. Spanner, R., in Verhandlungen der anatomischer Gesellschaft, Anat. Anz. (supp.) **85**:81, 1938.

35. Grafflin, A. L.: Anat. Rec. **57**:59, 1933.

36. Grafflin, A. L.: Anat. Rec. **68**:145, 1937. Marshall and Grafflin.[30]

basis for the varying, but low, glomerular function which can be demonstrated physiologically. However, considerable degeneration is already present in the youngest specimens examined, and these changes become steadily more prominent with increasing age. . . . This degeneration is interpreted as a physiological involution rather than as a pathological process.

Despite the widespread obliteration of the glomerulus and of its associated neck segment, the remainder of the nephron, consisting solely of the proximal tubule, almost uniformly persists. Furthermore, the persistent aglomerular nephrons are entirely normal in appearance, and in no single instance do they exhibit the marked hyperplastic changes observed in the proximal tubule in human nephritis.

It will be recalled that in his thesis Turley made the following statement concerning the hyperplastic nephrons in chronic nephritis: "The epithelium of the tubule as it leaves the glomerulus is reduced to a squamous form, and this change extends for a considerable distance along the tubule, to the twelfth turn in some cases studied." In his subsequent publication [2] he emphasized this observation, stating that "this was a uniform process in all of the compensating tubules and it was not an atrophy but a change to a different type of epithelium." Associated with the fact that the epithelium in this region is flattened is the fact (see page 697) that "the tubule remains the normal diameter for some distance from the glomerulus," subsequently showing a marked increase in diameter. The reason for emphasizing this observation of Turley's here is that no mention of the squamous character of the epithelium in the first portion of the proximal convoluted tubule is made in the original publication by Oliver and Lund [4] or in subsequent publications from Oliver's laboratory. However, there are indications that the latter workers have at times been dealing with the same thing in their maceration studies. For example, Oliver and Luey [5] stated that "the tubule contiguous to the glomerulus may remain undilated, thus forming a long narrow stretch that extends to the dilated portion." Here they refer to their figure 17, which, in gross appearance at least, suggests the condition described by Turley. Also, Loomis [6] stated that "the increase in the diameter of the proximal convoluted tubule is often less marked near the glomerulus."

While in his thesis Turley stated simply that there is "an enormous increase in the functioning capacity of one of these (hyperplastic) tubules over that of the normal tubule," in a later paper [37] he was more specific: "An idea of the extent of this compensatory hyperplasia can be gotten when we realize that some of these hyperplastic tubules judging by a comparison of the surface of the epithelium have the functional capacity of nine normal tubules." This is to be compared

37. Turley, L. A.: J. Oklahoma M. A. **14**:205, 1921.

with the statement of Oliver and Luey [5] that "the hypertrophied unit may replace in physical size twelve normal structures."

Turley's model includes a portion of the ascending limb of Henle's loop but not the distal convoluted tubule. In figure 2 *A* it can be seen that the ascending limb has been cut off at its point of apposition to the glomerulus. Turley identified the ascending limb belonging to the nephron by its close relationship to the vas afferens of the glomerulus. From the foregoing comment, this procedure would leave no doubt as to the accuracy of the identification, particularly in view of the report by Oliver and Luey [5] that the intimate association of the ascending limb with the glomerulus, characteristic of the normal kidney, is likewise true of the abnormal kidney.

The Illustrations.—All of the illustrations presented in this paper are new and, with the exception of figure 8, have been made in this laboratory under my direction. The legends for all figures are sufficiently explanatory, so that no further comment on them is necessary.

In Turley's original thesis there are four plates of illustrations, which will be briefly described. Plate I contains two photographs of the model of the normal nephron, a top view and a side view (the latter the same as figure 1 *A* in the present article). Plate II is a pencil drawing from the normal kidney, showing Bowman's capsule with the tubular outlet from it and cross sections of the proximal convoluted tubule, distal convoluted tubule and the ascending and descending limbs of Henle's loop. Plate III contains two photographs of the hyperplastic nephron in chronic nephritis, a top view (as in figure 2 *A* of this article) and a side view (but from the side opposite to that shown in figure 1 *B* of this article). Plate IV contains two pencil drawings labeled "hyperplastic tubules." One drawing shows Bowman's capsule with its tubular outlet, the latter exhibiting flattened epithelium, and cross sections of the proximal and distal convoluted tubules. The other drawing represents a transection of the loop of Henle, with cross sections of the ascending and descending limbs.

SUMMARY

Over twenty years ago Dr. Louis A. Turley made three plastic reconstructions of the human nephron, representing (1) the normal nephron, (2) the glomerulus and proximal convoluted tubule in acromegaly and (3) the hyperplastic nephron in chronic nephritis. These three plastic reconstructions are the subject of the present report. Turley's description of his findings is given in his own words, taken primarily from his doctoral thesis. Various aspects of his work are commented on in the light of present knowledge, and a fairly extensive series of photographs and drawings of the models is supplied. The model of the normal

nephron represents the only instance, up to the present time, in which the reconstruction of an essentially complete adult mammalian nephron, including the loop of Henle, has ever been successfully accomplished. The model of the glomerulus and proximal convoluted tubule in acromegaly is entirely unique; it demonstrates that the proximal convoluted tubule has undergone a striking increase in length, but not in diameter, and that the increase in length is roughly proportional to the enlargement of the kidney as a whole (approximately twice normal). The model of the hyperplastic nephron in chronic nephritis antedates by many years the recent model of Oliver and Lund and confirms, and to some extent supplements, their findings and the findings in maceration studies made by Oliver and Luey and by Loomis. The outstanding feature of the hyperplastic nephron is an enormous enlargement of the proximal tubule, affecting both the pars convoluta and the pars recta.

It has been known since the work of Golgi that the ascending limb of the loop of Henle applies itself to the glomerulus of the same nephron, lying in close apposition to the vascular pole. Contrary to Hamburger and Peter, who emphasized the close relationship of the ascending limb to the vas efferens, Turley was the first to appreciate that the essential relationship of the ascending limb is to the vas afferens.

ARRESTED PULMONARY COCCIDIOIDAL GRANULOMA

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AND
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For many years after the first case of coccidioidal granuloma was recognized,[1] infection by the fungus coccidioides (Coccidioides immitis) was considered to produce a progressive disease resulting uniformly in death unless the entire mass of infected tissue could be excised or at least thoroughly curetted.[2] However, in certain cases of coccidioidal granuloma in tissues like the leptomeninges or the joints infection must have occurred by metastasis, yet no primary focus is apparent. Four such cases of coccidioidal meningitis are included in the series of Abbott and Cutler.[3] This means either that the organisms can pass into the blood stream from the site of inoculation without producing recognizable lesions or that primary lesions may be nonprogressive and become so inconspicuous that they are missed even when carefully sought at postmortem examination. The latter possibility is supported by Abbott and Cutler's case in which the supposed primary lesion in the lung showed "remarkable degrees of healing." Giltner [4] reported apparent healing of coccidioidal granulomas produced in calves and pigs. Dickson's [5] collection of cases in man included an instance of "healed coccidioidal granuloma" of the lung. Further proof that coccidioidal infection may heal or become quiescent was afforded by Dickson [6] when he established the fungus coccidioides as the cause of a nonfatal respiratory disease associated with erythema nodosum. This disease, known as "valley fever," "desert fever" or "desert rheumatism," is prevalent in the San Joaquin Valley, Calif., where coccidioidal granuloma has long been

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2. Wolbach, S. B.: Boston M. & S. J. **172**:94, 1915.

3. Abbott, K. H., and Cutler, O. I.: Arch. Path. **21**:320, 1936.

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known to occur frequently. Moreover, increasing use of the coccidioidin skin test has revealed many positive reactions in persons who live or have lived in the San Joaquin Valley but who neither give a history of erythema nodosum nor show evidence of active coccidioidal granuloma.[7]

The present study is concerned only with quiescent granulomatous lesions of coccidioidal origin. We wish to emphasize, as did Dickson, that the lesions of "valley fever" have not been demonstrated to be coccidioidal granuloma in the sense that their histologic structure is granulomatous. Careful studies are still needed to determine the relationships between various manifestations of the fungus infection.

It is to be hoped that physicians throughout the country will acquire an interest in this disease, isolated cases of which have been reported repeatedly in various parts of the world. Most of these cases have been related to residence in California, but recently indications of an endemic distribution of the fungus coccidioides outside California have been recorded by Woolley [8] and by Farness.[9] These observers have seen several patients who while living in Arizona acquired mild respiratory symptoms and erythema nodosum and whose sputum gave cultures of the fungus coccidioides.[10] In view of the common occurrence of benign infection with the fungus coccidioides and the trend toward use of migratory labor in the San Joaquin Valley, as well as the extension of travel facilities within the United States and the increasing recognition of cases of this infection outside California, it seems timely to call attention to quiescent lesions due to this fungus which are likely to be passed over in postmortem examinations as tuberculous.

REPORT OF CASES

In the course of about 3,000 routine autopsies performed in San Francisco between the years 1932 and 1937 there were found 4 cases of arrested coccidioidal granuloma. In the same series there were an equal number of cases of progressive coccidioidal granuloma. It is probable that other arrested lesions were missed, since in 3 of the 4 instances which are reported here the diagnosis was first made by histologic examination of calcified nodules from the lungs or intrathoracic lymph nodes and since in many of the autopsies histologic sections from such nodules were not made as a routine. These facts indicate that cases of arrested coccidioidal granuloma in man are more frequent than is usually supposed and may considerably outnumber

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9. Farness, O. J.: Coccidioides Infection: Report of a Case Primary in the Lung with Cavity Formation and Healing, Am. Rev. Tuberc., to be published.

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the cases of fatal progressive granuloma. It should be noted particularly that the autopsies were performed in a district outside the San Joaquin Valley. There, where active lesions of this disease are frequent, the incidence of arrested lesions may be expected to be much higher than is indicated by their frequency in our autopsy series.

In all cases to be reported the patients were past 50 years of age. In 2 instances the occupation was such that there might have been unusual exposure to dust, but in only a single instance (case 4) was the patient known to have spent a period of time in the San Joaquin Valley. In no patient were the arrested coccidioidal lesions a factor in causing death.

CASE 1.—A 56 year old white miner had worked in dusty coal mines, as well as in gold and silver mines, for thirty-five years up to seven years before his death. Residence in the San Joaquin Valley was not recorded. He denied having had any severe illnesses. Roentgen studies of the chest three years before death showed a dense shadow about 2 cm. in diameter at the apex of the right lung and an indefinite faint shadow at the apex of the left lung.

At autopsy, performed the day after death, the anatomic diagnosis was: carcinoma of the lung with metastases to the tracheobronchial lymph nodes; bronchopneumonia; emphysema; arrested coccidioidal granuloma of the lungs.

A large infiltrating tumor almost replaced the lower lobe of the right lung, and at the bronchial bifurcation the lymph nodes were enlarged and grossly infiltrated with tumor. The posterior parts of both lungs showed extensive hyperemia, edema and pneumonia. In addition, there was a firm black nodule, about 2 cm. in diameter, in the lung substance near the apex of each lung. Each nodule contained a core of gray material, 1.4 cm. in diameter. There were no other scars.

Histologically, each of the two nodules from the upper lobes was composed largely of masses of partly calcified granular material, surrounded by a well demarcated dense fibrous capsule. The inner portion of this capsule was extensively hyalinized; the outer portion contained much black carbon pigment, scattered lymphocytes and several small nodules. The last mentioned varied in composition from hyalinized fibrous tissue to fibrous tubercles, in which epithelioid cells and occasional giant cells of the Langhans type were recognizable. However, there was no evidence of active extension of the process (fig. 1). Toward the periphery of the caseous material and embedded in the fibrous tissue at several points were a few scattered spherules from 15 to 40 microns in diameter. Each of these had a granular inner structure and a double-contoured refractile capsule characteristic of the fungus coccidioides. At the center of the caseous material were a number of empty refractile capsules like those of the intact spherules near the periphery. Calcified spherules were not seen, but some of the spherules present showed irregular thick capsules, the outer portions of which were nonrefractile and were stainable with eosin, giving the surface a ragged appearance. One spherule contained endospores (fig. 2). The hilar and mediastinal lymph nodes contained tumor tissue, and one node showed several small scars, but there was no evidence of coccidioidal infection.

Comment.—The character of the pulmonary nodules was not suspected in examination of the gross specimen, and no cultures were made. Of particular interest was the presence of a localized lesion in *each* lung with no evidence of

lymphatic spread. These lesions were comparable in size and position to the shadows seen in the roentgen films taken three years before death. At that time they were presumably already old, and apparently they underwent no significant change during the last three years of the patient's life. However, the presence of intact spherules in the lesions suggests that some organisms were still alive.

CASE 2.—This 66 year old Scotch deliveryman was seen over a period of two years before death, but an inadequate history was recorded, and it is not known whether he had lived in the San Joaquin Valley. Roentgen examination of the chest two years before death showed no abnormality of the lung fields. The

Fig. 1.—Low power magnification of the margin of one of the pulmonary nodules in case 1, showing the dense fibrous capsule and a small secondary nodule adjacent to a small artery at the outer surface. Hematoxylin–Van Gieson stain; × 13.

patient died following a colostomy performed to relieve a chronic obstruction of the large bowel.

Autopsy, performed eight hours after death, showed: diffuse hypertrophy of the colon without obstruction; bronchopneumonia; arteriosclerosis of the coronary arteries; arrested coccidioidal granuloma of the lung.

There was moderate bronchopneumonia in both lungs posteriorly, and at each apex was a moderate-sized dense fibrous scar. One was composed of an oval caseous central portion, 8 mm. long, and a capsule of dense black fibrous tissue, about 1 mm. thick.

Histologic examination showed many clusters of black pigment in the outer portion of the fibrous capsule, which was hyalinized and sharply demarcated from the adjacent lung tissue. It contained scattered clusters of lymphoid cells but no epithelioid or giant cells. The centrally located caseous material was granular and basophilic. It contained numerous long clefts resembling spaces from which crystals had been dissolved, and many easily recognizable spherules, from 15 to 30 microns in diameter, with double-contoured refractile capsules characteristic of the fungus coccidioides. Intimately attached to the outer surface of some spherules was an irregular thin layer of homogeneous, slightly basophilic material, which gave

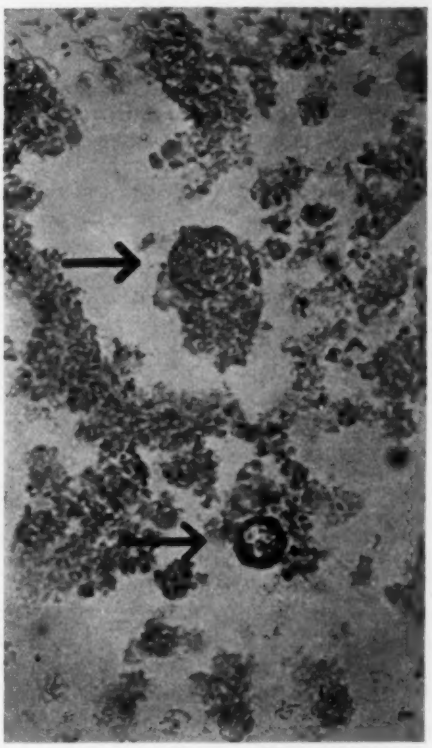

Fig. 2.—A portion of the caseous material from the nodule in case 1, showing a thin-walled spherule containing endospores and a smaller one with a thickened irregular capsule. Hematoxylin-eosin stain; × 490.

the surface a rough, ragged appearance. Near the periphery of the caseous zone were a few completely calcified spherules, stained deeply with hematoxylin. Two spherules were larger than the others, had thin capsules and contained numerous small round endospores characteristic of the fungus coccidioides.

Comment.—Since the unusual nature of the nodules in the lungs was not recognized during life or at autopsy, no cultures were made, no material was taken for histologic study from the fibrous area in the other lung, and no special search was made for abnormal lymph nodes within the thorax. However, none

was found on routine examination. Although the lesion described was completely arrested, one could not consider it healed, since numerous intact spherules were present. Presumably the calcified spherules were dead before the death of the patient, but many spherules deviated in appearance from those in fresh lesions only by the accumulation of an irregular thin homogeneous stainable layer on the surface of the capsule.

CASE 3.—A Greek insurance broker aged 53 years gave no history of residence in the San Joaquin Valley and remembered no serious illness prior to the onset of heart failure seventeen months before death. Roentgen examination of the chest was not made.

Autopsy, performed four hours after death, gave the following anatomic diagnosis: generalized arteriosclerosis, with hypertrophy of the heart and scars in the heart muscle; chronic passive hyperemia of the viscera; anasarca; chronic cholecystitis with calculi in the gallbladder; scar at the apex of the lung; arrested coccidioidal granuloma of a mediastinal lymph node.

The lungs showed no lesions aside from peripheral collapse and hyperemia, with a small superficial scar at the apex of the right lung, where there were a few fibrous pleural adhesions. The hilar lymph nodes were small and black, except for one which measured 2 by 1 by 1 cm., behind and to the right of the trachea, near its bifurcation. This node contained an irregular white caseous mass, about 7 mm. in greatest diameter, with a peripheral firm calcified portion and a thin but dense fibrous capsule.

Histologic study of this lesion showed a granular structure of the caseous material, in which were many slender fusiform clefts. Here and in many places within the inner portion of the fibrous capsule were many spherules with double-contoured refractile capsules, from 10 to 30 microns in diameter. In some the outer surface of the capsule was slightly ragged and irregular. Many capsules were empty, but others contained poorly defined refractile granular material, and some were calcified, showing a deep blue staining reaction with hematoxylin and lacking visible detail in their inner structure. No small endospores were found, but in two places spherules buried in the capsule enclosed daughter spherules up to 10 microns in diameter. The fibrous capsule was extensively hyalinized in its inner portion. In one place it had a nodular appearance, as if formed by fusion of several masses, but no cellular tubercles were present. Aside from a few scattered lymphocytes, the capsule contained few cells. It was sharply demarcated from the remaining lymphoid tissue.

Comment.—Presumably the portal of entry of the fungus was the lung, though no lesion was found except the apical scar, which was considered so characteristic of a tuberculous scar that no material was saved for histologic study. It did not grossly resemble any of the arrested lesions found in the other cases reported here. Conceivably, the pulmonary lesion was completely healed or had been reduced to such insignificant proportions that it was overlooked. Also, the possibility cannot be ruled out that the organism passed through the lung without producing a lesion. In any event, the lesion of the lymph node was completely arrested, as determined by its histologic structure, but, as in cases 1 and 2, the lesions cannot be considered healed.

CASE 4.—A 60 year old Yugoslavian farm hand came to California in 1917 and was employed on a hopper machine in the San Joaquin Valley. Soon he noticed on the dorsum of his right wrist an eczematous lesion. This became ulcerated and persisted until his death, fifteen years later, though during the

intervening years it had undergone stages of partial healing and exacerbation. On several occasions during the early course of this lesion cultures from it showed growth of Coccidioides immitis. The patient had no pulmonary symptoms except those associated with heart failure during the last two years of his life. However, a roentgenogram of his chest made two years before death showed several "round calcified areas of density the size of marbles" in both lower lung fields, with moderate increase in the hilar markings (fig. 3).

Autopsy was performed two days after death. The anatomic diagnosis was: generalized arteriosclerosis with hypertrophy of the heart and scars in the heart muscle; thrombosis of the renal artery with infarction of the kidney; arrested tuberculosis of a mesenteric lymph node; scars at the apexes of both lungs; arrested coccidioidal granuloma of the skin of the wrist and of the lungs.

The lesion of the wrist consisted of an irregular zone of thin, slightly uneven skin, pigmented light brown, about 3 cm. in diameter, the center of which was covered by a small crust. No pus was present, and no material was removed for histologic study. There were a few firm localized adhesions partly obliterat-

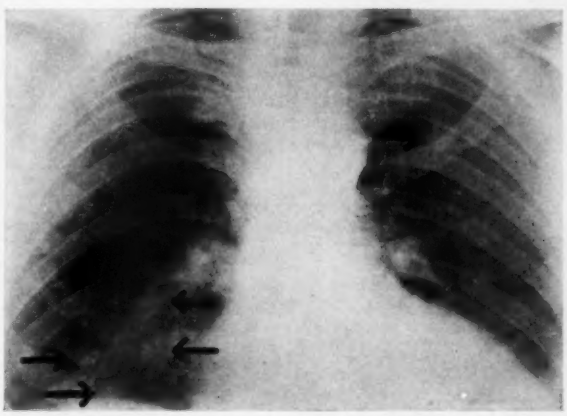

Fig. 3.—Roentgenogram of the chest (case 4) taken two years before death. There are well circumscribed areas of density in the lower portions of both lung fields.

ing the left pleural cavity posteriorly and covering a calcified subpleural nodule, about 1 cm. in diameter, near the upper margin of the lower lobe of the left lung posteriorly. There was a similar large node, measuring 3 by 2.5 by 2.5 cm., in the tissue of the same lower lobe anteriorly near the inferior margin, and two smaller, pea-sized nodules were found in the periphery of the upper lobe near its lower lateral margin. The right lung was bound to the parietal pleura anteriorly and inferiorly by fibrous adhesions and showed an easily visible scar at the apex. There were interlobar adhesions, and near the periphery of the middle lobe anteriorly was a nodule, 1 cm. in diameter, like those on the left. Two similar nodules, 1.5 cm. in diameter, were present anteriorly and posteriorly in the lower portion of the lower lobe. All of the nodules had sharply defined dense fibrous capsules, 1 to 2 mm. thick, and a central portion composed of dry white opaque grumous material, partially calcified (fig. 4). They were similar to the lesions described in the previous cases. There was no enlargement of the hilar lymph nodes. The mesentery contained a calcified mass, 1.5 by 0.8 by 0.8 cm., which

on histologic examination showed extensive caseation of the central portion and beginning ossification at the periphery, but no demonstrable bacteria or fungi.

Histologically the lesions in the lungs were sharply separated from the adjacent normal-appearing tissue by a dense fibrous tissue wall; the inner portion was extensively hyalinized. One of the lesions showed remnants of several fused smaller nodules. The central portions were made up of granular and amorphous material, stained extensively with hematoxylin and containing many slender clefts. There were a few free spherules with double-contoured refractile capsules, from 15 to 30 microns in diameter. Some were calcified and stained deep blue with hematoxylin, some were empty, and some contained poorly defined granular material. Several contained typical endospores of the fungus coccidioides. Cultures of material from the pulmonary lesions on Sabouraud's dextrose agar showed growth of mycelia identified as Coccidioides immitis. The fibrous capsule was infiltrated by a few lymphoid cells, but there were no tubercles or other evidence of active extension of the fungus infection. Occasional spherules were embedded in the hyaline portion of the fibrous capsule, but there was no local inflammatory reaction, and such organisms showed no endosporulation. Several peribronchial

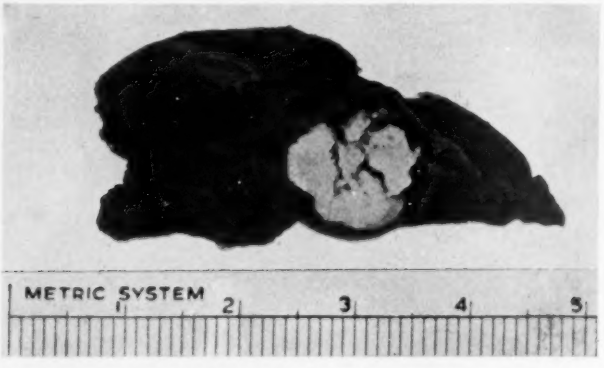

Fig. 4.—Section through a partially calcified caseous arrested coccidioidal granuloma of the lung (case 4).

lymph nodes were slightly enlarged, but no coccidioidal lesions were found. The calcified lesion in the mesentery, though structurally resembling the nodules in the lungs, contained no demonstrable organisms, so it was considered as probably the result of a primary tuberculous infection.

Comment.—Death was apparently due to circulatory failure and certainly was unrelated to the lesions produced by the fungus coccidioides. The relation between the lesion of the skin and those in the lungs cannot be decided with certainty. It is tempting to consider the cutaneous lesion as a primary focus from which organisms reached the lung by the blood stream or by lymphatic channels, but there was no history of an injury to the skin preceding the development of the lesion, and no evidence was found at any time to indicate disease of the axillary lymph nodes. Furthermore, similar lesions of the lungs were found in the preceding cases without any associated cutaneous lesions. We believe that secondary infection of the skin from a primary lesion of the lung is a likely possibility, though it is possible that a primary lesion of the skin had always remained localized, and the pulmonary process resulted from a separate infection of the respiratory tract. Regardless of the sequence of events in this case, it is prob-

able that the lesions in the lungs represented an infection of many years' duration, perhaps as long as fifteen years, the known duration of the cutaneous lesion. It is especially notable that cultures showed living organisms in this patient who had carried localized coccidioidal lesions for fifteen years.

EXPERIMENTAL OBSERVATIONS

In view of the obviously arrested nature of the lesions described, experiments were planned with a view to producing arrested lesions in animals. It was not our purpose to reproduce the human disease in all details or to evaluate the influence of immunity and allergy in the animals, though further studies are in progress in this direction.

Almost all experimental work heretofore reported in the literature, as well as that previously carried out in this institution, has been done by inoculating animals with quantities of material which were not accurately standardized, such as suspensions of material obtained from cultures. The lack of readily measurable units because of the presence of both mycelial filaments and chlamydospores makes accurate calibration of the inoculation difficult. Material obtained from pus from animal lesions offers a simpler means of estimation and calibration of the amount of infectious material to be inoculated. Here, owing to the occurrence of the organisms as spherules, it is possible to count directly the units in a given sample of pus and thus calculate the approximate number to be injected into a test animal.

In our experiments material for inoculation was obtained from testicular lesions in guinea pigs, each of which had been infected intratesticularly with 0.25 cc. of a saline suspension of a virulent culture of the fungus coccidioides (S. F. S. no. 46) grown on Sabouraud's medium. To estimate the concentration of spherules, a sample of diluted pus was filtered through sterile cotton and mixed with an equal volume of 10 per cent sodium hydroxide solution to dissolve débris, and the spherules in this cleared solution were counted in an ordinary blood counting chamber. Recently we have found that partial separation of the spherules from the other elements of pus can be obtained by centrifugating the diluted pus. The spherules accumulate at the bottom of the sediment in the centrifuge tube.

There are, of course, errors involved in such calibration of a suspension of spherules. Some spherules may be dead, and variations in the number of free endospores cannot be detected by counting spherules. However, our experience has shown such factors to be reasonably constant in different samples of the same pus and in pus from different animals, so that estimations of the number of growing units are all of the same order of magnitude.

Injection of the organisms into the venous circulation of young adult white rats was preferred to administration by surface application or inhalation, as it was felt that the number of spherules reaching the

tissues could be most accurately estimated in this way. Although the analogy to the arrested lesions in the cases observed in man is not exact, the lungs were predominantly affected in both man and animal, and in the experiments an advantage was gained by knowing that all injected organisms reached the tissues. The injections were made into the right side of the heart or into the jugular vein. Most of the animals were anesthetized for the injection with ether, though others were anesthetized by intraperitoneal injection of pentobarbital sodium. No difference in the development of lesions could be detected in these two groups of animals, so it has been assumed that a short exposure of the tissues to ether during narcosis does not affect the development of the fungus coccidioides within them. Further work has shown that rats differ very little in susceptibility from guinea pigs, which are well known to be highly susceptible to infection with this fungus.

Effect of Intravenous Inoculation of Spherules of Coccidioides

Spherules Injected	Animals	Average Duration of Life, Days	Loss of Weight
30,000 or more	6	9	Rapid
20,000	4	13	Rapid
10,000	2	48	Slow, continuous
5,000	5	*	Slight, transient
2,500	4	*	Slight, transient
1,000	5	*	Slight, transient
750 or less	20	*	Slight, transient

* After a few days the animals appeared normal and gained weight steadily. They died of causes unrelated to the granulomatous lesions, which were arrested. One exception is discussed in the text.

To determine approximately the susceptibility of the rats, calibrated suspensions of organisms were injected into 43 animals in the manner described. The inoculums ranged from 100 to 150,000 spherules. As is apparent from the accompanying table, the minimum fatal inoculum was 10,000 spherules. The lungs of animals receiving fatal inoculums uniformly showed extensive coccidioidal granuloma. One animal which had received 1,000 spherules lost weight and died three weeks after infection. Its lungs showed widespread coccidioidal lesions. This was the only animal of those receiving 5,000 spherules or less whose death could be attributed to coccidioidal granuloma. Three animals which had received small inoculums died within two months of secondary infections, but in these the coccidioidal lesions were not extensive. With exclusion of these 4 animals, 21 rats which received 1,000 spherules or less survived periods averaging four hundred and thirty-nine days per rat, with no significant difference related to the dose. One rat became pregnant and produced a normal litter without showing any evidence of disease.

Granulomatous lesions containing spherules of the fungus coccidioides were found in all of the 21 animals but 2. One of these, which had received 500 spherules and died after two hundred and forty days, was not examined post mortem. The other showed no granulomatous lesions on careful gross and histologic study of the organs three months after injection of 100 spherules. The lungs of the other 19 animals all showed irregular yellowish to white opaque nodules from 1 to 3 mm. in diameter (fig. 4). These were most numerous at the pleural surface and were readily visible before the lungs were sectioned, but, in spite of this relation to the pleura, in only a few instances were there any pleural adhesions. The mediastinal lymph nodes were enlarged in most animals, and a few contained grossly visible, poorly defined small white opaque nodules.

Accurate counts of the number of lesions found in the lungs of the different animals were not made, since some of the lesions were confluent and there was sometimes difficulty in distinguishing grossly between specific granulomatous nodules and small scars or abscesses in the lungs due to other causes. It was noted, however, that there was a correlation between the number of spherules injected and the number of lesions produced, though the number of lesions was always smaller than the estimated number of spherules. In some instances not more than 10 per cent of the estimated spherules were represented by nodules in the lungs.

In order to study the evolution of the fibrous nodules without introduction of differences in size of the inoculums as a confusing factor, a second group of 33 rats was inoculated in the manner already described. Each animal received 200 spherules by right-sided intracardiac injection. Twelve animals were put to death during the first four months. Eighteen were examined post mortem at approximately monthly intervals during the succeeding fourteen months. Three were studied at nineteen, twenty-two and twenty-nine months, respectively. Eight of the animals died of secondary infections during the period of observation, but, although the appearance of the lungs was frequently altered by pneumonia, the structure of the granulomatous lesions was not appreciably different from that in the animals which were put to death.

Two animals, which lived for one and seven months, respectively, after inoculation, showed no gross or microscopic lesions in the lungs, mediastinal lymph nodes, spleen, kidneys, liver, heart or testis. The reason for the failure of the organisms to proliferate is not known. Thirty-one of the animals showed lesions in the lungs grossly like those described in the previous series, though there was quite striking variation in the number of gross lesions in different rats. This was unrelated to the time following inoculation. Presumably it was a manifestation of varying degrees of resistance in different animals.

Nature of the Lesions.—Within two weeks after inoculation, nodular lesions from 1 to 2 mm. in diameter had developed in the lungs, due to the accumulation of masses of epithelioid cells, among which were a few giant cells of the Langhans type. These nodules were irregular in contour, owing to conglomeration of smaller cellular tubercles. In the larger lesions caseous necrosis of the central part had occurred, and the necrotic areas contained disintegrating polymorphonuclear leukocytes and nuclear débris. A broad zone of lymphocyte and macrophage infiltration containing scattered eosinophilic leukocytes surrounded the epithelioid cell masses at this stage. Spherules of the fungus coccidioides in all stages of development were abundant not only in the central

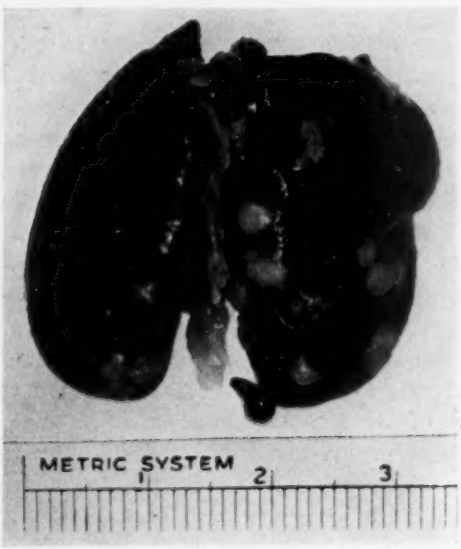

Fig. 5.—Lungs of an adult white rat fourteen months after intravenous inoculation of 1,000 spherules of the fungus coccidioides.

portions of these lesions but also among the epithelioid cells throughout all portions of the tubercles and within giant cells.

In animals killed a longer time after inoculation the conglomerate nature of the nodules was more marked, suggesting that spread of the lesions had continued after the first two weeks. At two months significant amounts of collagen could be seen among the epithelioid cells in the tubercles, which had become distinctly less cellular. Abundant lymphoid cells were still grouped peripherally about the nodules, and spherules of the fungus coccidioides were scattered throughout all parts of the tubercles (fig. 5).

A gradual increase in the amount of collagen with an accompanying decrease in cellularity and a decrease in the degree of peripheral lymphocytic infiltration occurred during the remainder of the twenty-nine month period of observation. Calcification of the caseous material was observed in about one third of the animals killed five months or more after inoculation. In the lesions nine months old definite localization of the spherules to the centers of the tubercles was noted. This became more pronounced as the lesions became older until, after two years, most of the spherules were deeply embedded in the fibrous tissue of the

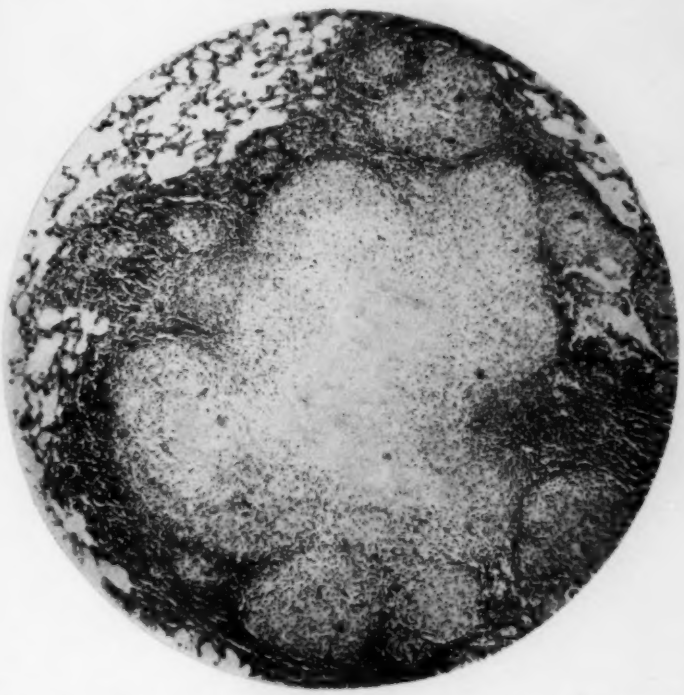

Fig. 6.—Experimental coccidioidal granuloma two months old in the lung of a white rat. Hematoxylin-eosin stain; × 57.

nodules (fig. 6). This gave the impression that the organisms were mechanically limited in their growth by the dense fibrous tissue of the nodules. Another interesting appearance, presumably due to mechanical limitation of the growth of the organisms, was that of three generations of spherules growing one within another (fig. 7). This was seen frequently in the older experimental lesions, though it was not certainly identified in the human lesions. Figure 7 also shows striking irregularity in the size of developing sister spherules from endospores within a single old shell, another common observation in the old lesions. A third char-

acteristic of the spherules in the old lesions, and one which was also present in the human cases, was a thickening of the capsule, the outer surface of which frequently had an irregular, ragged appearance due to a layer of slightly eosinophilic material unlike the refractile substance forming the inner portion of the capsule.

The oldest lesions were distinctly larger than those a few months old, and they showed the most extensive conglomeration of small noncaseous tubercles, as well as the least caseation. In many the peripheral tubercles in a conglomerate nodule were obviously more cellular than those more

Fig. 7.—Experimental coccidioidal granuloma twenty-two months old in the lung of a rat. The lesion is composed largely of hyalinized fibrous tissue and shows little evidence of inflammation, but spherules of the fungus are abundant. Hematoxylin-eosin; × 57.

centrally placed, and it was noted occasionally even in the oldest lesions that a few spherules existed in tissue completely outside the fibrous nodules. Such spherules were enclosed by giant cells. This indicates that even though the infection is controlled, a limited spread of the organisms may occur. Since the lesions in animals dying of pneumonia or some other complication were not appreciably different from those in animals which were put to death, such spread cannot be considered a flare-up during a secondary infection.

In 29 of the 31 animals with pulmonary coccidioidal granuloma the mediastinal lymph nodes showed lesions. These lesions were similar to those in the corresponding lungs, indicating that they developed coincidentally with the lesions in the lungs. The structure of some of the lesions in the lymph nodes likewise suggested a slow local spread.

Cultures were made from the granulomatous lesions in 12 animals of the first series and 23 of the second series by grinding one or more excised nodules in a mortar and planting the material obtained on

Fig. 8.—Experimental coccidioidal granuloma (high power magnification of the lesion shown in figure 7). Three generations of spherules are seen limited to one region. At the edge of the group of well developed spherules are refractile remnants of an old capsule. The endospores in two of the spherules represent the third generation.

Sabouraud's dextrose agar. Sixteen of the cultures were from animals which had lived longer than twelve months following inoculation. One had survived two and a half years. In 31 instances there was growth of the fungus coccidioides from the lesions in the lungs; in 2, growth occurred from nodules from lymph nodes but not from those from the lung, while in 2 others cultures produced no growth of fungus.

One of these concerned an animal which died with extensive bronchopneumonia seven months after inoculation of 200 spherules. Histologic study of the lungs from this animal showed that the lesion which had been cultured was a pyogenic abscess with a fibrous wall, while lesions due to the fungus were quite small and may not have been included in the material cultured. The second negative culture was obtained from an animal which had been killed two months after inoculation. No explanation can be given for the failure of the organisms to grow. It can be seen that with two possible exceptions all of the animals harbored viable fungi and that living organisms remained in the lesions for as long as two and a half years. This again emphasizes the fact that although the lesions were arrested, they cannot be considered to have healed.

GENERAL COMMENT

In the 4 cases of arrested coccidioidal granuloma in man which are reported in this paper there was no characteristic position of the lesions in the lungs. They occurred as frequently in the upper as in the lower lobes. Each was near the periphery of the lung, but all did not lie immediately beneath the pleura. Definite involvement of lymph nodes was demonstrable only in case 3, in which the only lesion found was in a large lymph node at the hilus of the lung. It is possible, however, that one or more of the nodules in case 4 represented completely destroyed lymph nodes in the lung substance. The lesions uniformly consisted of relatively large central masses of partially calcified caseous material with surrounding sharply outlined capsules of dense hyalinized connective tissue. In 2 cases small fibrous tubercles were present in the capsules, and most of the lesions were lobulated, suggesting that they had been formed as conglomerate nodules. It is possible that smaller lesions with less prominent central caseous areas may result from arrest or healing of coccidioidal granuloma. Such lesions may be easily missed at autopsy, since they cannot be distinguished grossly from arrested or healed lesions of tuberculosis.

Specific organisms were cultured in only a single case of the series in man, but in the others the presence of numerous characteristic spherules in histologic sections permits only the diagnosis of coccidioidal granuloma. Although some of the spherules were calcified and others showed no internal structure, in every lesion there were spherules resembling those seen in actively progressive coccidioidal granuloma, and in each case a few spherules contained endospores. This strongly suggests that viable organisms were present, as was proved in case 4 by culture and by animal inoculation. Whether spread of the fungus occurs from such arrested lesions cannot be decided from our human material, but evidence that the organisms readily enter lymphatic vessels

is afforded by our experimentally inoculated animals, more than 90 per cent of which showed secondary infection of mediastinal lymph nodes. It is probable that caseous lesions are sometimes sources of massive infection of the blood stream, as has been demonstrated in cases of tuberculosis. It is our opinion that the arrested lesions, whether in the lungs or in the lymph nodes, constitute potential sources of widespread infection.

The influence of allergy and immunity in the formation of arrested lesions cannot be deduced from the appearance of the lesions in our cases, nor can it be stated with certainty whether these lesions represented primary or secondary infections. In a number of respects they resembled the reaction of the tissues to a primary tuberculous infection: The pulmonary lesions were localized; they were situated peripherally in the lungs, without constant relationship to the apexes; caseation of the lesions in lymph nodes was prominent in 1 case, and all lesions showed extensive central caseation with calcification. The hematogenous route of infection of the lungs cannot be assumed for most cases in man, though the history of case 4 suggests that the infection of the lung may have been hematogenous.

The arrested lesions produced by intravenous inoculation of rats with small numbers of spherules of the fungus coccidioides were comparable to the lesions found in man so far as they were localized pulmonary lesions which contained viable fungi and were associated with similar lesions in the regional lymph nodes. The formation of conglomerate nodules was much more prominent in the lungs of the rats, whereas caseation in old lesions was less extensive in the rats than in man. However, the experimental lesions of long duration had striking basic similarities to the lesions in human lungs.

Although no evidence was obtained that the number of spherules in a minimum fatal inoculum differed widely in different animals, there was a definite indication of difference in response of individual rats to a small inoculum of 200 spherules. A similar individual variation in response to infection in man may reasonably be expected.

SUMMARY

Four cases of completely arrested coccidioidal granuloma of the lungs or of the bronchial lymph nodes in man are reported. In none of these were the granulomatous lesions a factor in the cause of death.

Similar arrested lesions could be produced at will by injecting small numbers of spherules of a virulent strain of the fungus coccidioides intravenously into white rats or guinea pigs. The minimum fatal inoculum for rats inoculated in this way was approximately 10,000 spherules.

In nearly all the arrested experimental lesions organisms remained viable for periods up to two and a half years. In a human case organisms were cultured fifteen years after they had been first demonstrated.

It is concluded that instances of arrested coccidioidal granuloma are more frequent than has heretofore been realized, that they probably outnumber the fatal cases of this disease and that they are not restricted to the region of the San Joaquin Valley, Calif. The relationship of arrested coccidioidal granuloma to the benign clinical disease known as "valley fever" is as yet unknown. Although the lesions present a histologic picture of inactivity, they may contain viable fungi for many years and constitute a possible source of dissemination.

Case Reports

DIVERTICULA OF THE VERMIFORM APPENDIX ASSOCIATED WITH AN OVERGROWTH OF NERVE TISSUE AND A PARTIAL MUCOCELE

JACOB R. DORDICK, M.D., NEW YORK

One finds very few cases of diverticula [1] of the vermiform appendix recorded in the literature up to 1907.[2] This is not astonishing because at or about this time the clinical and pathologic concepts of appendicitis were first being molded.[3] Since then, several excellent reviews have been presented.[4] The authors of these reviews, utilizing for the most part surgical material, collected 86 instances. To date, a total of 126 cases have been recorded.[5] This probably does not represent all the cases, since many may not have been reported.

The case reported now warrants presentation because of the large number of closely placed diverticula, the unusual overgrowth of nerve tissue and the partial mucocele. I have been unable to find any record of a similar one in the literature.

From the Department of Pathology, Beth Israel Hospital.

1. The term "diverticula" is used here for convenience sake, without regard to completeness or incompleteness of the layers forming the wall.

2. Isabelle Herb was able at that time to collect 25 instances from the literature (Tr. Chicago Path. Soc. **7**:94, 1907).

3. Kelly, H. A., and Hurdon, E.: The Vermiform Appendix and Its Diseases, Philadelphia, W. B. Saunders & Company, 1905. Murphy, J. B.: J. A. M. A. **22**:302, 1894.

4. (*a*) McCarty, W. C., and McGrath, B. F.: Surg., Gynec. & Obst. **12**: 211, 1911. (*b*) Moschcowitz, E.: Ann. Surg. **63**:697, 1916. (*c*) Stout, A. P.: Arch Surg. **6**:793, 1923. (*d*) Mulsow, F. W.: ibid. **24**:923, 1932. (*e*) Edwards, H. C.: Brit. J. Surg. **22**:88, 1934. (*f*) Sauer, P. K.: Am. J. Surg. **10**:564, 1930. (*g*) Collins, D. C.: Ann. Surg. **104**:1001, 1936.

5. (*a*) Seelig, M. G.: Ann. Surg. **44**:78, 1906. (*b*) Schweizer, R.: Virchows Arch. f. path. Anat. **185**:278, 1906. (*c*) Konjetzny, G. E.: München. med. Wchnschr. **56**:2251, 1909. (*d*) Simon, W. V.: Berl. klin. Wchnschr. **48**: 1501, 1911. (*e*) Krabbel, M.: Beitr. z. klin. Chir. **80**:121, 1912. (*f*) Wilkie, O. P. D.: Brit. J. Surg. **8**:392, 1921. (*g*) Löhr, W.: Deutsche Ztschr. f. Chir. **171**:30, 1922. (*h*) Chase, W. H.: Canad. M. A. J. **17**:416, 1927. (*i*) Gordham, A. J.; Choyce, C. C., and Randall, M.: Brit. J. Surg. **16**:62, 1928. (*j*) Pack, G. T., and Scharnagel, I.: Am. J. Surg. **58**:369, 1928. (*k*) Walmsley, T.: J. Anat. **64**:47, 1929. (*l*) Stewart, J. D.: New England J. Med. **203**:1288, 1930. (*m*) Kline, L. B.: Mil. Surgeon **77**:275, 1935.

REPORT OF CASE

A 29 year old white woman, married and a housewife, had always been in perfect health until eight months prior to operation, when intermittent cramp-like pains in the lower quadrant of the abdomen set in. There were no other symptoms. The menstrual history was not unusual. There was no fever at any time. The results of the physical examination were entirely negative except that some tenderness was found in the right lower quadrant of the abdomen.

After consultation with several physicians, Dr. I. W. Held advised an appendectomy. The patient was operated on Dec. 5, 1932. The postoperative course was uneventful. She has remained in good health to the present time, five years after operation.

Gross Description of Specimen.—The specimen was an appendix, approximately 9 cm. long. In the proximal half, it was normal in thickness. The tip was slightly club shaped and measured 2.1 cm. across. The fat tissue of the mesentery was adherent to the appendix and appeared normal. In the distal half, eight irregularly round and ovoid protrusions were seen in the serosa (fig. 1 *A*). Five were situated close to each other, opposite or nearly opposite the attachment of the mesentery; the remainder appeared on the mesenteric border. The largest protrusion, which was cystic, measured 7 by 3 by 3 mm. Several of the smaller protrusions were opaque. There was no evidence of acute inflammation.

A longitudinal section of the appendix showed that the cavity of the aforementioned larger protrusion was in direct continuity with the lumen of the appendix (fig. 1 *A*). This section, although passing nearly exactly through the middle, did not open a continuous lumen. In the 2 cm. near the tip, three small, irregularly round cavities were seen, one being continuous with the lumen of the larger cystic protrusion mentioned. It contained glassy mucoid material. These lesions corresponded to the protrusions found on the antimesenteric border of the appendix.

The three protrusions on the mesenteric border of the appendix, on closer outside examination, already were recognized as fat lobules. On the cut surface, they roughly overlay three solid polypoid herniations, 3.5 mm. apart and approximately 2 mm. in diameter. On this longitudinally bisected specimen the muscle coat was about 2 mm. thick and glassy gray. On the side of the solid protrusions, the cut edge was represented by partly round, partly elliptic markings separated from each other by strands of opaque grayish-white tissue. These strands continued in the direction of the mesentery, thus forming the solid polypoid herniations described. On the opposite side, the muscle coat was thicker and interrupted by two wide gaps, corresponding to the cystic protrusions (fig. 1 *B*).

Microscopic Description.—The microscopic picture was as unusual as the gross. The larger cavity situated in one of the protrusions was a mucocele, the tip of which was separated from the serosa of the appendix by only a thin layer of fibrosed submucosa. It contained much partly laminated mucoid material (the mucicarmine stain was positive).

The lumen of the appendix was narrow. The mucosa, as far as it was preserved, was not unusual. There were a moderate number of long and many more short glands. Goblet cells, for the most part, were few. Except for a sparsity of lymphocytes, the cellular pattern of the mucosa was not remarkable. The lymphatic follicles were few and small but otherwise normal.

The submucosa was thicker than normal, was rather densely fibrous and contained much more nerve tissue than one would expect.

The muscle coat was not continuous. It was separated into segments by the submucosal tissue, which protruded through wide gaps. Between the gaps, both muscular layers were seen. The round protruding masses of submucosal tissue

directly bordered on the serosa. Occasionally thin remnants of muscle tissue (visible only on higher magnification) were stretched over the convexity of the diverticula (fig. 2). The elastic tissue was preserved. The subserosa and serosa were not unusual.

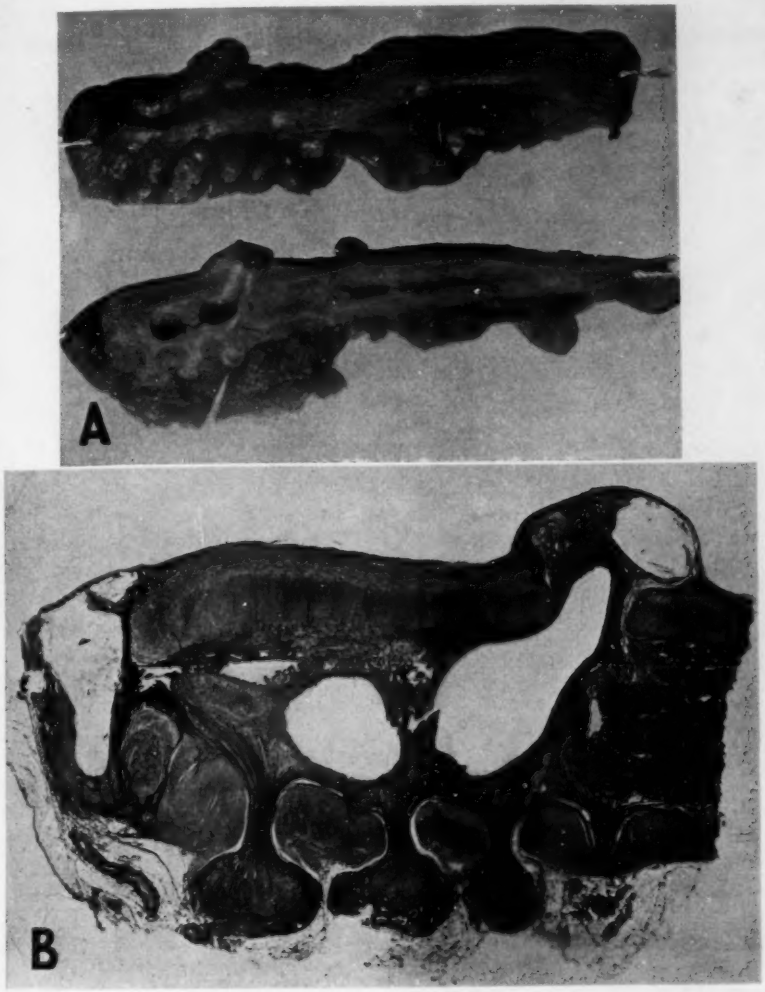

Fig. 1.—*A*, the exterior surface and a longitudinal section of the appendix, showing different types of protrusions and their relationship to the mesentery. *B*, the long section under very low magnification. In the central upper portion, the muscle coat appears unbroken. To the right and left, diverticula are seen. Their mucosal lining cannot be recognized at this magnification. In the lower portion, the muscle coat is broken up. Dense masses of submucosa reach through wide gaps in the muscle and spread in polypoid fashion. They are surrounded by fat tissue. At the right lower corner, the section has gone obliquely through the narrow pedicle of one protrusion.

The solid protrusions consisted essentially of submucosal connective tissue with many blood vessels and an enormous amount of nerve tissue (fig. 2). The nerve tissue predominated to such an extent that in the sections stained by Van Gieson's method it could be seen with the naked eye. There was no overgrowth of ganglion cells.

The inside of each cystic protrusion was mostly lined by a single layer of columnar cuboidal or flattened epithelial cells, under which some traces of lymphoid tissue were found. In the mucocele-like portion, no mucosa was seen. The mucus had separated the innermost layers of the surrounding wall.

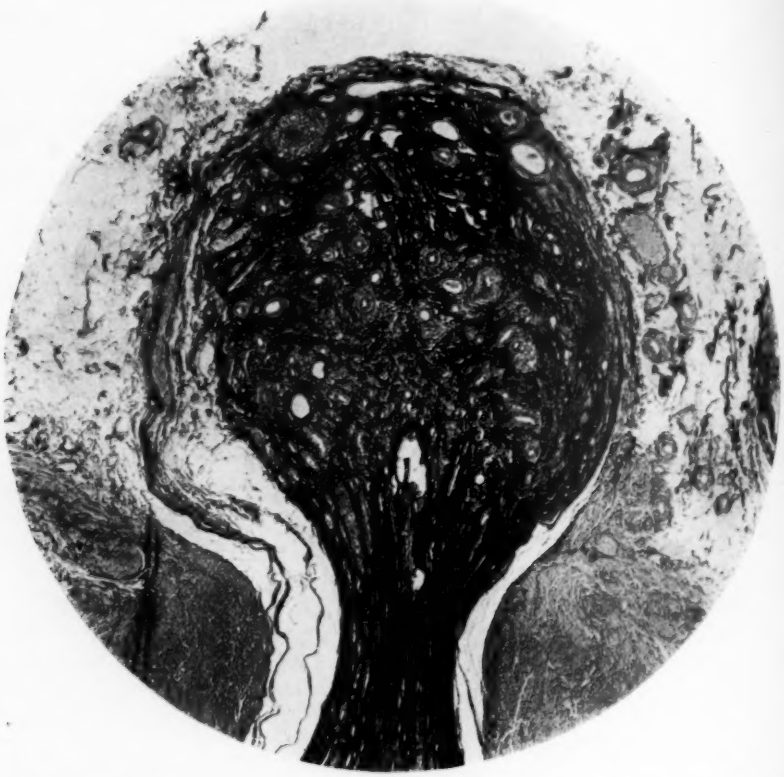

Fig. 2.—High magnification of a solid protrusion, showing the presence of neuromas and diffuse hyperplasia of nerve tissue. Thin remnants of muscle surround the diverticulum. Note the overgrowth of nerve tissue in the vascular connective tissue of the submucosa.

COMMENT

Although new interest in this lesion has recently appeared, diverticula of the vermiform appendix probably occur more commonly than one would judge from the available reports.[51] No doubt many more cases would be recognized were a longitudinal section of the appendix,

passing through the mesenteric border,[6] or many cross sections examined. Another factor responsible for the low reported incidence is the failure of this condition to produce clinical symptoms.

Yet one should not minimize the complications that may ensue. When acute inflammation of the appendix sets in, rapid perforation of the thin-walled diverticula may occur after only a few hours of vague abdominal symptoms.[4g] A review of the surgical literature gives percentages from 39 [4e] to 100 [4b] for the occurrence of acute inflammation in appendixes that are the seat of diverticula. These figures, no doubt, would be much lower were the appendixes in which diverticula were found accidentally at autopsy included in these statistics. When the diverticula are associated with mucocele, as in the present case, perforation with the development of pseudomyxoma peritonei is not an unusual finding.[5i] Diverticula of the vermiform appendix occasionally have perforated into other viscera, with the formation of fecal fistulas.[4d]

The theories regarding the genesis of the multiple diverticulum are almost as numerous as the observers reviewing the subject. Weakness of the muscular wall, either congenital or acquired, plus increased internal pressure, was mentioned at one time as the causative factor.[7] Mertens [8] observed that diverticula pass through arterial gaps in the muscular wall of the appendix. Aschoff [9] and later Chase [5h] held that the loss of fat and fibrous tissue about these vascular gaps could cause definite weakness at a point later the site of a diverticulum. Mulsow [4d] maintained that continuous traction from without, as by adhesions, may ultimately produce diverticula.

The role of antecedent inflammation in the genesis of diverticula has been emphasized by many observers.[10] Some maintain that it is the sole etiologic agent.[11] While one cannot deny that a preceding intramural abscess with destruction of the muscularis, followed by healing and cicatrization, may leave a locus minoris resistentiae at which herniation of the submucosa may occur, one is not justified in assuming that it is the only underlying factor. For surely, in many of these appendixes, even a careful study fails to reveal recent or old inflammation. In the case reported here and in 6 others collected over nine years at the Beth Israel Hospital, no inflammation was found. The lumen of the appendix in the specimen described in this report was uniformly narrow, but no local point of obstruction was encountered.

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6 Moschcowitz.[4b] Stout.[4c]

7. Heschl: Wien. med. Wchnschr. **30**:540, 1880. Beer, E. H.: Am. J. M. Sc. **128**:135, 1904.

8. Mertens, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **9**:743, 1902.

9. Aschoff, L.: Spezielle pathologische Anatomie, in Pathologische Anatomie: Ein Lehrbuch für Studierende und Aerzte, ed. 3, Jena, Gustav Fischer, 1913, vol. 2, p. 824.

10. Moschcowitz.[4b] Edwards.[4e] Sauer.[4f] Collins.[4g]

11. Mundt, T.: Ueber Veränderungen der Muskelwand des Wurmfortsatzes, in Pathologische-anatomische Arbeiten: Herren Geh. Medicinalrath Dr. Johannes Orth zur Feier seines 25jährigen Professor-Jubiläums, Berlin, A. Hirschwald, 1903, pp. 463-470. Moiroud, P., and Imbert, R.: Bull. et mém. Soc. nat. de chir. **58**:732, 1932. Moschcowitz.[4b] Edwards.[4e]

Christeller [12] subdivided diverticula of the appendix into two categories, namely, those at sites of previous inflammation and not caused by mechanical factors, such as narrowing of the lumen and increase of internal pressure, and those caused by mechanical factors such as those mentioned. In the latter group, the narrowing may be due to postinflammatory scarring or to a noninflammatory process. The case I have reported would fit into the latter classification, the narrowing being unrelated to any inflammatory changes.

Stout [4c] suggested that the contractions of the circular and longitudinal muscle coats are the chief active factors in driving mucosa and submucosa through a weakened point in the muscularis. In a series of controlled experiments on the dog's appendix he found that operative muscular defects resulted immediately in protrusion of mucosa and submucosa. This was accompanied by active contractions of the circular and longitudinal muscles. When the muscles had lost their contractility, no protrusions occurred provided the lumen remained patent. The experimental defects were much larger than the corresponding spontaneous defects in the human patient, and certainly they were formed much more rapidly.

As previously mentioned, none of the case reports contains any description of the neuromatous change in the diverticula.[13] Neuroma of the appendix is much more frequent than most physicians realize. In the material at the Beth Israel Hospital, every second appendix examined (when a sufficient number of sections is taken) shows neuroma. Other authors give similar, some even higher, figures. Of 344 consecutive appendixes examined by Hosoi,[14] 195 (56.7 per cent) showed nerve lesions. In a similar study Simard [15] found that neuroma occurs in 75.2 per cent of obliterated appendixes. Fein, Hanan and Seider [16] reported 202 neuromas in a series of 600 consecutive appendixes (an incidence of 33 per cent).

In view of the obscure etiologic background of both the diverticula and the neuroma, it is not astonishing that I am unable to explain their simultaneous occurrence in this specimen. As long as the problem of "chronic appendicitis" remains unsolved, one cannot expect to understand the possible connection between chronic inflammatory processes in the appendix and the occurrence of herniation through the vascular gaps. Moreover, none of the theories given in the literature, in my opinion, adequately explains the formation of diverticula of the vermiform appendix.

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12. Christeller, E., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, pt. 3.

13. A recently described case (Wunder, E.: Frankfurt. Ztschr. f. Path. **51**: 18, 1937) bears a certain similarity to the one I have reported except for the fact that no neuromatous change is mentioned. It concerned a 39 year old man who had vague abdominal pain, tending to localize in the right lower quadrant. In the appendix, partly cystic, partly solid diverticula were found.

14. Hosoi, E.: Arch. Path. **16**:500, 1933.

15. Simard, L. C.: Canad. M. A. J. **33**:518, 1935.

16. Fein, M. J.; Hanan, J. T., and Seider, V. B.: Am. J. Surg. **40**:120, 1938.

SUMMARY

In the appendix of a 29 year old woman who had presented vague abdominal symptoms, 8 partly cystic, partly solid diverticula were found. One of the cystic protrusions gave the picture of a partial mucocele. A diffuse neuromatous lesion occupied most of the submucosa in the solid diverticula.

No record of a similar case could be found in the literature.

COARCTATION OF THE AORTA OF THE ADULT TYPE, ASSOCIATED WITH CYSTIC DEGENERATION OF THE MEDIA IN THE FIRST PORTION OF THE ARCH

F. F. Harrison, M.D., Cooperstown, N. Y.

Coarctation of the aorta is not a particularly unusual congenital cardiovascular anomaly. According to autopsy statistics collected by Blackford,[1] it occurs once in about 1,550 cases. The present case seems worthy of note, however, because of the fact that during the patient's lifetime it was carefully studied and reported from a physiologic standpoint [2] and also because the microscopic observations in the aorta are of considerable interest.

REPORT OF CASE

A medical student 27 years of age was admitted to the hospital June 11, 1935. Eleven years previously he had been found to have a systolic blood pressure of 185 mm. and signs of endocarditis. The correct diagnosis, however, was not made until his entrance into medical school in 1931. At this time roentgen examination of the chest showed scalloping of the inferior borders of the ribs, and there were characteristic signs of coarctation of the aorta, together with an associated aortic insufficiency. The condition was then well compensated. Two years later, in collaboration with Grollman [2] he published a study of his own cardiac output. The final illness began with an infection of the upper part of the respiratory tract three weeks before admission. An exacerbation of this infection four days before admission iniatited a rapid break in cardiac compensation.

The temperature was 102 F.; the pulse rate, 120; the respiratory rate, 24. The blood pressure in the right arm was 148 systolic and 70 diastolic; that in the left arm, 180 systolic and 70 diastolic; that in the legs, 98 systolic and 70 diastolic.

The patient appeared desperately sick, with marked pallor, diaphoresis and extreme dyspnea. The heart was tremendously enlarged, with loud systolic and diastolic murmurs. There were dulness, increased breath sounds and moist rales at the base of the left lung. The laboratory findings were all essentially negative. A roentgenogram showed scalloping of the inferior margins of the ribs and a huge heart. He died in less than forty-eight hours after admission.

Autopsy.—The panniculus was scanty; the musculature, well developed and deep red. The superior epigastric arteries were unusually large and apparently anastomosed with the internal mammary and inferior hypogastric arteries. The lower border of the liver lay 11 cm. below the xiphoid process and 5 cm. below the right costal margin in the nipple line. The spleen was somewhat enlarged but was well above the costal margin.

From the Department of Pathology, Mary Imogene Bassett Hospital.

1. Blackford, L. M.: Arch. Int. Med. **41**:702, 1928.
2. Grollman, A., and Ferrigan, J. P.: Arch. Int. Med. **53**:35, 1934.

Both lungs were collapsed and lay well back in each side of the thoracic cage. There was no free fluid in either pleural cavity. The pericardial cavity contained the usual amount of straw-colored fluid.

The heart and the aorta weighed 932 Gm. The epicardial surface was smooth. There was a fibrous tag near the apex of the heart. All four chambers of the heart were widely dilated and filled with clotted blood. The right and left anterior aortic leaflets showed some thickening and rolling downward of the free edges, and on the right anterior leaflet there was a small gelatinous-appearing nodule, possibly 1 mm. in diameter. The wall of the right ventricle measured 8 mm. in thickness; that of the left, 26 mm. The right coronary artery had a double origin, one component of which was small.

The circumference of the aorta was found to be as follows:

	External	Internal
At attachment of cusps		12 cm.
6 cm. above cusps	8.5 cm.	7 cm.
At innominate artery	7 cm.	6.5 cm.
Between left carotid and left subclavian arteries	4.5 cm.	4 cm.
Just beyond left subclavian artery	4 cm.	3.5 cm.
At coarctation	3.2 cm.	0
At celiac axis	4.5 cm.	3.7 cm.
At bifurcation of aorta		2.0 cm.

The ascending part of the aortic arch was widened into an oval-shaped bulbous enlargement. This narrowed rapidly at a point 4 cm. above its origin, and then gradually until the coarctation was reached. The narrowest point of the aorta was about 7 mm. beyond a nonpatent fibrous cord representing the ductus arteriosus.

There was a slight amount of atheroma of the ascending aorta, which became more marked just above the coarctation. No lumen could be demonstrated at the point of coarctation, and just below it the atheroma was again only slight. The aorta beyond this point continued to be markedly narrowed as indicated in the measurements.

The collateral circulation of the occluded aorta seems to have been accounted for largely by the internal mammary, transverse cervical and transverse scapular arteries. The first-named vessels were very large, the lumen before fixation being nearly 5 mm. in diameter. The intercostal branches from the internal mammary arteries were small down to the fifth interspace. In the fifth and sixth interspaces large branches were given off. Below this point the vessels passed into the substance of the rectus muscle, where an anastomosis was formed with the deep epigastric artery.

The right lung weighed 425 Gm.; it was crepitant throughout; the parenchyma was rusty brown and quite dry.

The left lung weighed 350 Gm. Its general appearance was much like that of the right. The whole lower lobe felt somewhat boggy, and over the posterior aspect of the pleural surface a small amount of fibrin was deposited. At the inferior anterior border of this lung, in about the anterior axillary line, there was a large infarct, measuring about 8 by 6 cm. in its greatest diameters. On section there was a little more moisture in this lower lobe than in its fellow, but no actual areas of consolidation were made out.

The spleen weighed 260 Gm. In the hilus were two accessory spleens. The organ presented gross evidences of chronic passive congestion.

The liver together with the gallbladder weighed 1,925 Gm. They appeared grossly normal.

The stomach, intestines, pancreas and adrenals also appeared grossly normal.

Each kidney weighed 175 Gm. In the midportion of the left kidney was a small infarct, and the capsule stripped with some difficulty.

The pelvis, ureters and bladder presented no abnormalities. The genitalia appeared grossly normal.

Blood cultures showed no growth after incubation for ten days.

Microscopic Examination.—The individual myocardial fibers showed marked hypertrophy. The sections were studded with small areas in which an increase in

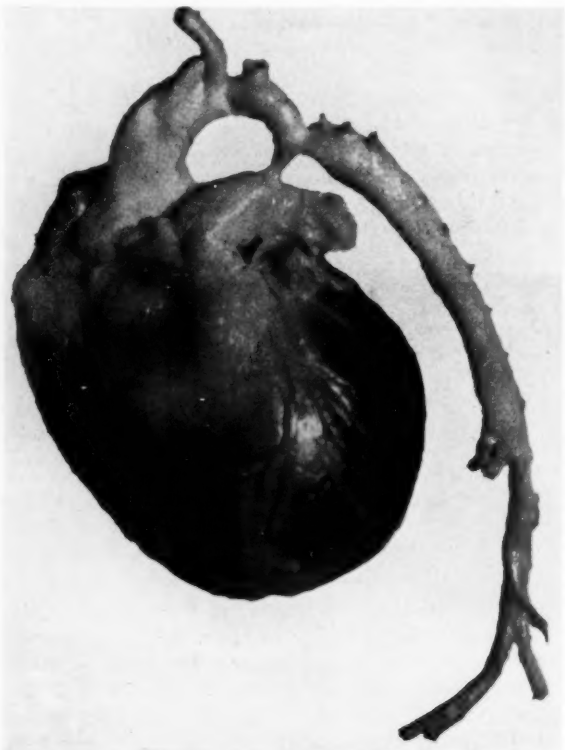


Fig. 1.—Heart and aorta.

fibrous connective tissue was apparent. This change was particularly notable in the immediate vicinity of the smaller branches of the coronary arteries.

The nodule on the end of the right anterior cusp of the aortic valve was bordered by dense connective tissue, within which there was a zone of less dense, rather myxomatous-looking tissue, containing two more or less rounded masses of acellular material. There was no evidence of a recent inflammatory reaction, and no organisms could be demonstrated with bacterial stains.

Sections through the first portion of the aorta showed well marked changes characteristic of atherosclerosis. A considerable amount of calcium was deposited in the half of the media adjacent to the intima. Deeper in the media many fibers appeared swollen, and often they were fragmented, with cystic areas between them, usually filled with mucinous-looking material. There was practically com-

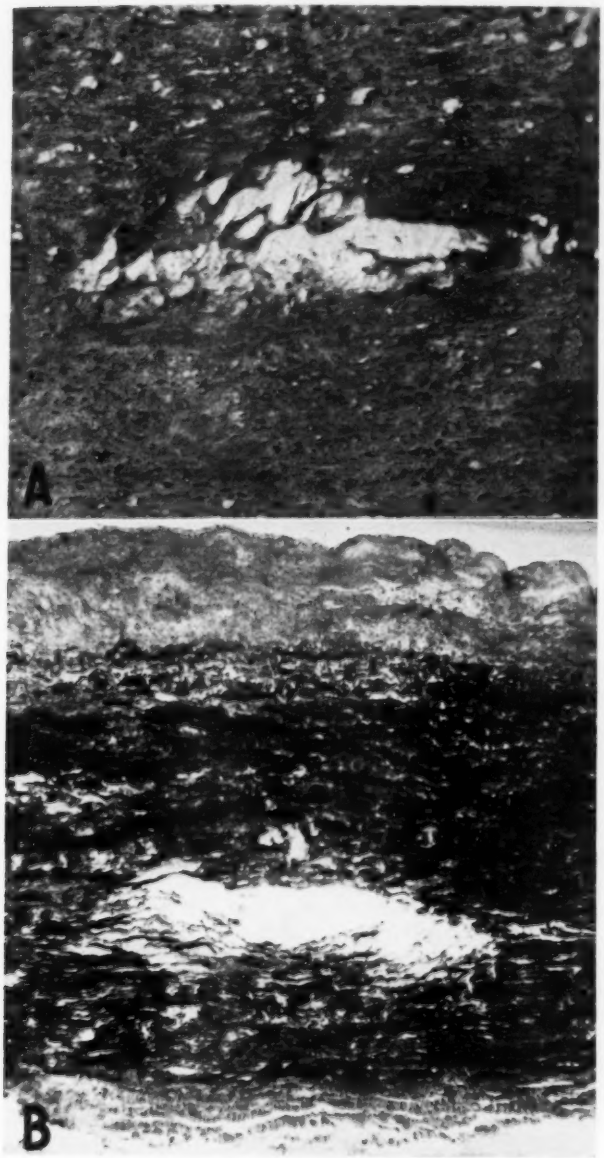


Fig. 2.—*A*, first portion of the aorta, showing a cystic area in the outer half of the media. Hematoxylin-eosin stain; × 250. *B*, first portion of the aorta, showing cystic area in outer half of the media; Mallory's aniline blue stain; × 150.

plete absence of cellular reaction in these areas. With the aid of stains for elastic tissue one obtained the impression that one of the earlier events was swelling and dissolution of collagen fibers, the elastic fibers at first remaining intact. Later, as the cavity thus created grew larger, the broken ends of the elastic fibers protruded into it. Still later they lay as fragments in the midst of the myxomatous material and eventually disappeared. At several points well preserved nuclei of smooth muscle could be demonstrated in the substance of the pronglike projections into the cystic cavities.

A section of aorta taken from a point near the origin of the left subclavian artery showed nothing unusual other than a moderate deposition of calcium in the media. In a block taken 1 inch (2.5 cm.) below the point of coarctation, however, rather marked atheromatous intimal changes were again apparent.

The sections of lung showed marked chronic passive congestion. One section taken from the infarcted area showed typical obliteration of the architecture with great numbers of red cells.

Sections of the spleen showed evidences of chronic passive congestion. The liver showed well marked evidence of chronic passive congestion and, in addition, a moderate amount of fatty infiltration in the midzonal region. Only the liver cells immediately adjacent to the portal spaces appeared normal. The kidneys and adrenals showed nothing unusual other than congestion.

The thyroid gland showed a moderate increase in connective tissue stroma. There was no evidence of activity of the gland.

Anatomic Diagnosis.—The following conditions were observed: coarctation of the aorta of the adult type, with complete atresia of the lumen; fibrosis of the coronary cusps of the aortic valve, with insufficiency; cardiac hypertrophy and dilatation; atheroma of the aorta; cystic medial degeneration of the aorta; acute fibrinous pleuritis; infarct of the lower lobe of the left lung and of the left kidney; general chronic passive congestion of the viscera; fatty infiltration of the liver.

COMMENT

Aneurysm of the aorta, almost always involving the first portion, is not uncommonly associated with coarctation and is frequently the cause of death. The descriptions of the histologic picture in the aorta have been most thorough in the cases in which rupture occurred. Bronson and Sutherland [3] reported an instance of coarctation with rupture of a fusiform aneurysm into the pericardium in a boy of 5. They described the degenerative changes as occurring predominantly in the outer part of the intima and the subjacent inner half of the media. They assumed that there had been two factors: (1) a congenital defect in the wall and (2) so-called protective sclerosis, resulting from the increased tension.

Blackford [1] held that the occurrence of rupture of the aorta in some cases in which stenosis was slight lends support to the idea that there existed in these instances an imperfect development of the wall of the aorta. On the other hand, the fact that in the greatest number of instances rupture occurred during or immediately subsequent to strenuous exertion tends to emphasize the factor of mechanical strain. A case in which mechanical strain could not have been a factor is that reported by Smith and Targett.[4] In this instance the aneurysmal

3. Bronson, E., and Sutherland, G. A.: Brit. J. Child. Dis. **15**:241, 1918.

4. Smith, F. J., and Targett, J. H.: Tr. Path. Soc. London **48**:53, 1896-1897.

opening was situated one-half inch beyond the coarctation. They described a thinning of the wall with a disproportionate loss of elastic fibers at and just above the coarctation. At the aneurysm there was an abrupt rupture of elastic fibers, with fraying of the broken ends.

Medial degeneration of the type found in my case is generally conceded to be the most common cause of dissecting aneurysm. An excellent report of cases of this type was published by Tyson.[5] The report includes 5 cases. One was probably a case of aneurysm due to syphilis. Marked degenerative changes in the media were found in the ascending aorta in all 5 cases. Associated with these changes was marked intimal thickening of the vasa vasorum in the adventitia. The most detailed descriptions of nonsyphilitic degenerative disease are those in the two papers published by Erdheim.[6] He emphasized the fact that in the disappearance of tissue the elastic fibrils were most conspicuously involved, the connective tissue less and muscle least. Great stress was laid on the absence of cellular exudate—a notable feature in my case as well. In contrast with Tyson,[5] Erdheim dismisses the possibility that disease of the vasa vasorum is an etiologic factor.

In the present instance it is quite possible that the association of coarctation with cystic degeneration of the media may have been wholly fortuitous. On the other hand, this association raises the question whether rupture of the aorta, which occurs with fair frequency in cases of coarctation, may not often have such a lesion as its pathologic basis.

SUMMARY

A case of coarctation of the aorta of the adult type is reported in a man who died at the age of 27 of rapidly developing cardiac failure. Associated with the coarctation was not only disease of the aortic valves but also dilatation and cystic medial degeneration of the first portion of the aorta.

5. Tyson, M. D.: Am. J. Path. **7**:581, 1931.

6. Erdheim, J.: Virchows Arch. f. path. Anat. **273**:454, 1929; **276**:187, 1930.

COMPLETE ANURIA DUE TO BLOCKAGE OF RENAL TUBULES BY PROTEIN CASTS IN A CASE OF MULTIPLE MYELOMA

RUSSELL L. HOLMAN, M. D., CHAPEL HILL, N. C.

Disturbances in renal function associated with excretion of protein in cases of multiple myeloma have been commented on by numerous observers,[1] but so far as I am aware no case of complete anuria due to this condition has been reported. None of the standard references consulted [2] lists anuria as a possible complication of multiple myeloma. The case reported here is of interest because of the extreme degree of obstruction of the renal tubular system by protein casts. Both the clinical data and the histologic appearance of the kidneys indicated that the precipitation of the abnormal protein occurred extensively within a relatively short period of time. The view expressed recently by Forbus, Perlzweig, Parfentjev and Burwell [1b] that the damage associated with excretion of Bence Jones protein is due primarily to mechanical obstruction and not to any specific toxic effect on the tubular epithelium is supported by this case.

A colored housemaid aged 43, married, entered the Presbyterian Hospital, New York, on May 4, 1936, complaining of pain in the right thigh of three weeks' duration. The familial and past histories were irrelevant. She had not menstruated for seven months. For three months there had been progressively increasing fatigue, weakness, insomnia and anorexia, with loss of 32 pounds (14.5 Kg.) in weight. Three weeks before admission pain began in the region of the right hip and increased in severity until walking became unbearable.

From the Department of Pathology, College of Physicians and Surgeons, Columbia University.

1. (*a*) Decastello, A.: Ztschr. f. klin. Med. **67**:319, 1909. (*b*) Forbus, W. D.; Perlzweig, W. A.; Parfentjev, I. A., and Burwell, J. C., Jr.: Bull. Johns Hopkins Hosp. **57**:47, 1935. (*c*) Groat, W. A., and Brewer, R. K.: J. Lab. & Clin. Med. **1**:895, 1916. (*d*) Hopkins, F. G., and Savory, H.: J. Physiol. **42**:189, 1911. (*e*) Jacobson, V. C.: J. Urol. **1**:167, 1917.

2. Allbutt, T. C., and Rolleston, H. D.: System of Medicine, London, Macmillan & Co., 1909. Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1936. French, H.: Index of Differential Diagnosis, Baltimore, William Wood & Company, 1935. Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929. Osler, W., and McCrae, T.: Modern Medicine, New York, Lea Bros. & Co., 1907. Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1937. Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1922.

Laboratory Data on Blood and Urine

	Blood								Fluids		Urine						
			White Blood Cells			Serum											
Date (1936)	Hemoglobin Percentage (Sahli)	Red Blood Cells, Millions	Total Count	Polymorphonuclears, per Cent	Monocytes, per Cent	Protein, Mg. in 100 Cc.	Albumin-Globulin Ratio	Nonprotein Nitrogen, Mg. in 100 Cc.	Daily Average Intake, Cc.	Daily Average Output, Cc.	Reaction	Specific Gravity	Albumin	Casts	Red Blood Cells per High Power Field	White Blood Cells	Bence-Jones Protein
May 4-17	62	3.3	5,600	25	75	8.0	0.7	29	Not recorded		Acid	1.025	+	Few	2-5	Loaded	.....
May 18-31	49	2.7	8,160	50	50	...	...	...	Not recorded		Acid	1.026	+	Few	1-2	Loaded	None
June 1-14	45	2.2	3,950	61	39	...	...	...	Not recorded		Neutral	1.015	++	Many	0	Few	.....
June 15-28	46	2.2	3,800	73	27	...	...	...	Not recorded		Acid	1.012	+++	Many	8	Loaded	.....
June 29 to July 12	44	2.5	2,900	59	41	6.4	1.0	150	1,600	12	Alkaline	1.010	++++	None	3-8	Many	None (2 examinations)
July 14	26	1.3	.....	..	..	...	...	156	2,000	±	Acid	Quantity insufficient	+	None	0	4 per high power field	None
July 17	24	0.9	1,200	69	31	...	...	...	0	0	Complete anuria since July 14						
July 22	24	1.1	1,200	63	37	...	...	167	0	0							

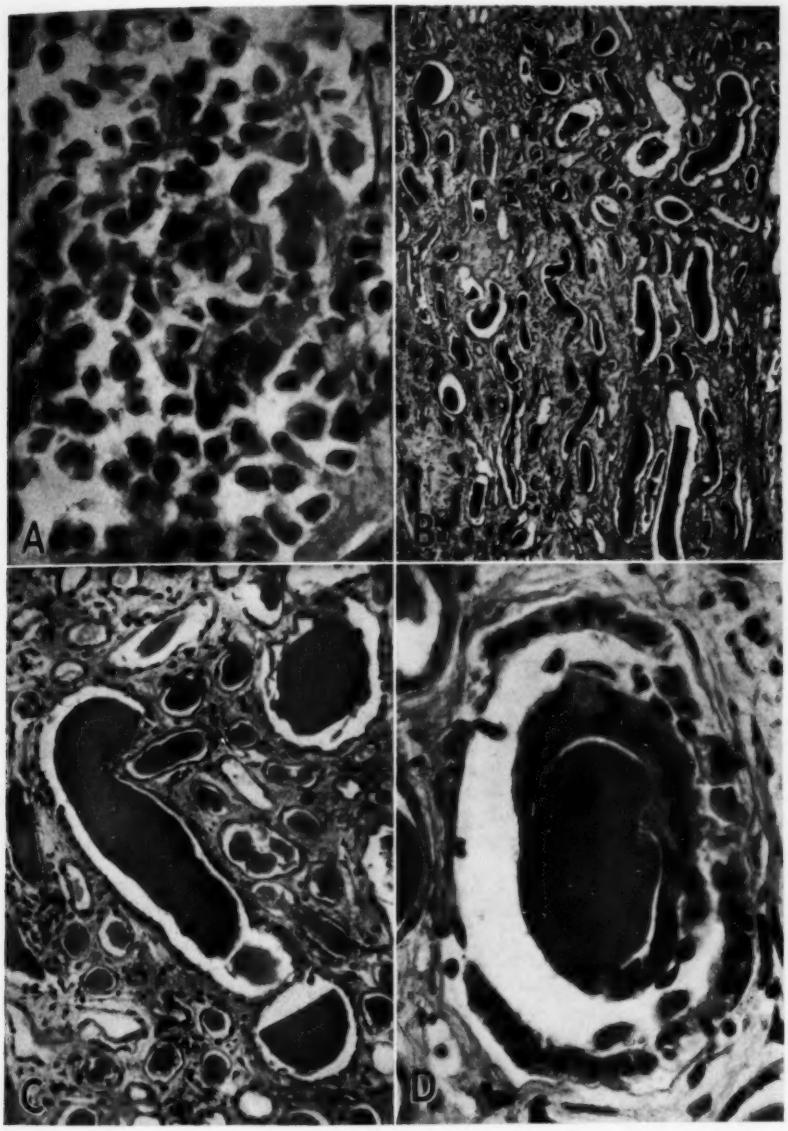
The temperature was 99.4 F.; the pulse rate 90, the respiratory rate, 18; the blood pressure, 102 systolic and 66 diastolic. No other abnormality was noted save the evidence of loss in weight and the pain on hyperextension of the right thigh. The laboratory findings pertaining to the blood and urine are summarized in the table. The Wassermann reaction of the blood was negative, and gastric analysis gave negative results. The erythrocyte sedimentation rate was from 80 to 164 mm. in an hour. The reticulocyte percentage on June 9 was 1. The bleeding time on July 5 was 12 minutes. Roentgenograms of the gastrointestinal tract, made with the aid of a barium sulfate enema, revealed no abnormality. Roentgenograms of the right leg, pelvis, spine, chest and sinuses on May 5 disclosed no lesions.

From the time of admission the patient presented a diagnostic problem. The first intimation of an organic lesion appeared in a roentgenogram of the spine, right hip and thigh taken on June 1; this showed an area of diminished density in the neck of the right femur. Similar lesions were seen later in the tenth dorsal and some of the lumbar vertebrae. Cystoscopic and pyelographic examinations on June 12 revealed no abnormality. Roentgen rays of high voltage were directed to the right hip in a course of treatments started on June 16; there was occasional vomiting following these treatments. Oliguria occurred from July 2 to July 14 and anuria from July 15 to July 23, the cause of which was never discovered. The patient's bladder was catheterized on July 13, but only a few cubic centimeters of urine was obtained. Parenteral injections of saline and dextrose solutions were started on July 5, and the amounts injected were increased until as much as 4,350 cc. was being given on July 13. These injections were discontinued after July 15. With the administration of the fluids mentioned, the patient became edematous and—as can be seen from the table—hydremic. The nonprotein nitrogen of the blood increased rapidly to 167 mg. in 100 cc. The patient died in uremia on July 23. No definite clinical diagnosis was made; suggestions were (1) lymphoblastoma, site unknown; (2) Hodgkin's disease, site unknown; (3) multiple myeloma.

Necropsy was performed twenty-two and one-half hours post mortem. The resultant diagnoses other than those directly related to the kidneys were: multiple myeloma (plasma cell type) involving vertebrae (ninth and tenth dorsal and third lumbar as shown in A in figure), the sternum, the neck of the right femur and the left parietal pleura; secondary myeloma in the liver; aplasia of the femoral bone marrow; hemosiderosis and extramedullary erythropoiesis in the spleen and liver; fatty infiltration of the heart; edema of the lungs; bilateral hydrothorax; ascites; edema of the hands and eyelids; acute and chronic cystitis; myomas of the uterus.

The kidneys were identical in appearance. Each weighed 180 Gm. The capsule stripped easily, disclosing a very pale gray surface. The cut surface was also pale gray. The cortex was of uniform width and measured 0.6 cm.; the cortical striations, though blurred, could be made out. The pyramids were sharply defined, and the pyramidal striations were distinct. The blood vessels appeared normal. The mucosa of the renal pelvis was slightly congested. The ureters were normal. In the bladder were only a few cubic centimeters of slightly turbid yellow urine.

Histologic examination disclosed that all the loops of Henle, the distal convoluted tubules and the collecting tubules were filled with dense hyaline casts (*B* in figure); about the margins of some of these were foreign body giant cells (*D* in figure) similar to those pictured by Forbus and his co-workers and claimed by them to be "specifically indicative of Bence-Jones proteinuria." The glomeruli appeared normal except for distention of the spaces of Bowman and slight thicken-



A, plasma cell myeloma in a vertebra; high power magnification; hematoxylin and eosin stain. *B*, protein casts in renal tubules; low power magnification; frozen section stained with sudan III. *C*, distention of tubules by casts; medium power magnification; hematoxylin and eosin stain. *D*, foreign body giant cell about a protein cast in a renal tubule; high power magnification; hematoxylin and eosin stain.

ing of the capsular basement membranes. The proximal convoluted tubules were dilated and the lining epithelium flattened. The remaining portions of the tubules were also slightly dilated; in some of them the cast distended the lumen to more than twice its normal diameter (*C* in figure). These tubules were lined by flattened epithelium. The interstitial tissue was edematous and here and there infiltrated by large mononuclear cells in clusters. Some of these cells resembled myeloma cells seen elsewhere but could not be definitely identified as such. The blood vessels were normal. The epithelial cells of the pelvic mucosa had desquamated; the basement membrane was everywhere intact. In the underlying stroma were groups of cells similar to those described between the tubules. There was no exudate on the mucosal surface of the urinary bladder. The mucosal stroma was edematous and congested and was diffusely infiltrated with mononuclear and polymorphonuclear leukocytes. No organisms were seen in a section stained by Gram's method.

COMMENT

As can be seen from the photomicrographs, the essential lesion was a typical myeloma of the plasma cell type. The chief interest in the case is the effect produced on the kidney by the abnormal protein being excreted. The only proof that this protein was of the Bence Jones variety was the presence of giant cells of the foreign body type about some of the casts in the renal tubules.[1b] The urine had been tested for this protein on four occasions, but none was found. It is well known, however, that the excretion of Bence Jones protein may be intermittent and that this protein is not found in the urine in every instance of multiple myeloma. Whatever name may be applied to the protein in the urine of this patient, it is obvious that one of its peculiar properties was coagulability. The protein apparently passed through the glomeruli without leaving histologic evidence of damage and first became solidified in the loops of Henle or more distal parts of the tubular system. Whether this was a consequence of reabsorption of water in the proximal convoluted tubules, with resultant increase in the concentration of the protein, or whether it was related to a change in the concentration of hydrogen ions or of electrolytes [1c] in the urine is conjectural. The result of the deposition of this protein was a mechanical blockage of the tubular system. The absence of detectable changes in the glomeruli with the dilatation of the spaces of Bowman and of the proximal convoluted tubules further supports the view that the damage was due to mechanical obstruction and not to any specific toxic effect of the abnormal protein on the tubular epithelium.

SUMMARY

A colored woman of 43 years died in uremia after twelve days of marked oliguria, followed by nine days of complete anuria. Terminally the nonprotein nitrogen of the blood rose to 167 mg. in 100 cc. All the renal tubules beginning with Henle's loop were plugged with hyaline casts. About the margins of some of these casts were foreign body giant cells. The proximal convoluted tubules and the spaces of Bowman were dilated. Since no other cause for the anuria could be found, it is assumed that it resulted from the mechanical obstruction.

Dr. Walter Palmer gave me permission to abstract the clinical data on this case.

General Reviews

HYPERPARATHYROIDISM AND RENAL DISEASE

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As knowledge of the function and of abnormal conditions of the parathyroid glands has rapidly increased in recent years it has become evident that there is a close linkage of these glands with renal function and disease. It is now known that lesions in the skeletal system are not the only important changes associated with hyperparathyroidism. In many cases renal disease may overshadow the skeletal changes. MacCallum [1] first drew attention to this relationship in 1905, when he reported a tumor of a parathyroid gland associated with chronic renal disease. Since that time many scattered reports have indicated a relationship between hyperparathyroidism and disease of the kidney. Much of the credit for knowledge of this subject must be given to Albright and his associates [2] for their numerous careful studies on this phase of hyperparathyroidism. Considerable confusion of terminology and etiology has resulted, however, partly because investigators are still not certain of the stimuli, normal or pathologic, which induce parathyroid secretion or of the mechanism of the action of this secretion.

In the present review an attempt will be made to survey reported studies which have a bearing on the problem of a relationship between increased parathyroid function and renal disease. It is hoped that a marshaling together of various case reports, experimental studies and

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1. MacCallum, W. G.: Bull. Johns Hopkins Hosp. **16**:87, 1905.

2. (*a*) Albright, F.: M. Clin. North America **18**:1109, 1935; (*b*) New England J. Med. **217**:1063, 1937; (*c*) Tr. A. Am. Physicians **51**:199, 1936; (*d*) **52**:171, 1937; (*e*) Internat. Clin. **3**:280, 1937. (*f*) Albright, F.; Aub, J. C., and Bauer, W.: J. A. M. A. **102**:1276, 1934. (*g*) Albright, F.; Bauer, W.; Cockrill, J. R., and Ellsworth, R.: J. Clin. Investigation **9**:659, 1931. (*h*) Albright, F., and Bloomberg, E.: Tr. Am. A. Genito-Urin. Surgeons **27**:195, 1934; (*i*) J. Urol. **34**:1, 1935. (*j*) Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Am. J. M. Sc. **187**:49, 1934. (*k*) Albright, F.; Bloomberg, E.; Castleman, B., and Churchill, E. D.: Arch. Int. Med. **54**:315, 1934. (*l*) Albright, F.; Drake, T. G., and Sulkowitch, H. W.: Bull. Johns Hopkins Hosp. **60**:377, 1937. (*m*) Albright, F.; Sulkowitch, H. W., and Bloomberg, E.: Am. J. M. Sc. **193**:800, 1937; (*n*) Arch. Int. Med. **62**:199, 1938.

theories may clarify research in this subject, point out gaps in knowledge and suggest lines along which future work may be profitable. As far as is consistent with intelligent consideration of the subject only those aspects of hyperparathyroidism which are directly related to renal function and disease will be considered.

Two facts stand out and at first seem confusing: 1. Primary renal disease may result in parathyroid hyperplasia and hyperfunction, the degree and effects of which are modified in individual cases by the severity of the renal deficiency and by factors influencing the metabolism of calcium and phosphorus.

2. Hyperparathyroidism, whether arising primarily in a functioning neoplasm of the parathyroids or secondarily in response to some stimulus from elsewhere, may produce renal damage varying from slight to severe also modified by other factors in addition to the severity of the hyperparathyroidism. In these relationships disturbances in the metabolism of calcium and phosphorus play a prominent part.

RELATIONSHIPS BETWEEN PARATHYROID AND RENAL FUNCTIONS

It has long been established that the parathyroid glands play an essential part in the metabolism of calcium and phosphorus and regulate their concentration in the serum. The point of action of the parathyroid hormone in the mechanism of this regulation has been a matter of some dispute. Approximately half of the normal 9 to 11 mg. of calcium in 100 cc. of serum is held in an inactive nondiffusible compound, bound in some way to serum protein. The remaining ionized portion is normally maintained within a relatively narrow range by parathyroid regulation. Fluctuation in the serum protein may cause considerable variation in the total serum calcium without the ionized, parathyroid-regulated portion varying beyond normal limits. Conversely, determinations of the total calcium may reveal no abnormality although the concentration of the ionized fraction is such as to indicate considerable disturbance of parathyroid function. The concentration of calcium ions in the plasma at any one time is the resultant of an equilibrium between the total calcium and the total protein present in the plasma. It is thus evident that, for significance regarding the parathyroids, any determination of serum calcium must take into account the level of plasma proteins. An increase in the concentration of phosphates in the serum may bring about a lowering of the ionized calcium. In hypoparathyroidism and hyperparathyroidism serum calcium and phosphorus maintain a relationship such that their product remains roughly constant except at high levels of serum calcium, when the phosphorus may rise abruptly. A third factor of importance is the alkalinity of the serum.

Albright,[2c] Goadby and Stacey [3] and Ellsworth and others [4a, b] noted that one of the early and prominent effects of injection of parathyroid extract is a phosphate diuresis. This increased excretion of phosphates is independent of the concentration of inorganic phosphorus in the blood plasma. Goadby and Stacey [3a] pointed out that there are three possibilities as to the point of action of the parathyroid hormone: (1) the mechanism of the kidney's excretion of inorganic phosphates, (2) the renal phosphatase and (3) the inorganic phosphorus of the blood or tissues. Their later investigations showed that in patients with severe impairment of renal function the phosphate diuresis was impaired or failed to appear. On improvement of renal function—as after recovery from an attack of acute nephritis—the phosphate diuresis again increased. It thus appears that the parathyroid hormone may act directly on the kidneys to allow increased excretion of phosphorus, resulting in a lowering of the serum phosphorus and a reciprocal rise in serum calcium. The matter would be simplified if it were not for evidence of other effects of the parathyroid hormone. However, Thomson and Pugsley,[5] Selye [6] and Thomson and Collip [7] found that the parathyroid hormone may directly stimulate osteoclasts to mobilize calcium from the bones and that this characteristic skeletal effect may be obtained even after bilateral nephrectomy. McJunkin, Tweedy and McNamara [8] also showed this characteristic osteoclastic reaction after bilateral nephrectomy but found that the increase of serum calcium which usually accompanies injection of parathyroid extract was not obtained. They suggested that in the nephrectomized animal, in which the serum phosphorus rises, the mobilized calcium does not accumulate in the blood because of increased elimination by the intestinal route. Ellsworth and Futcher,[4b] on the other hand, were able by injection of parathyroid extract to obtain increased serum calcium in bilaterally nephrectomized animals.

While this seems rather confusing, it appears to establish that there are at least two points at which parathyroid extract may have an effect on calcium metabolism. Since one of these effects is dependent on integrity of renal function, it is not surprising that disturbance of renal

3. Goadby, H. K., and Stacey, R. S.: (*a*) Biochem. J. **28**:2092, 1934; (*b*) **30**: 269, 1936.

4. (*a*) Ellsworth, R.: J. Clin. Investigation **11**:1011, 1932. (*b*) Ellsworth, R., and Futcher, P. H.: Bull. Johns Hopkins Hosp. **57**:91, 1935. (*c*) Ellsworth, R., and Howard, J. E.: ibid. **55**:296, 1934.

5. Thomson, D. L., and Pugsley, L. I.: Am. J. Physiol. **102**:350, 1932.

6. Selye, H.: Endocrinology **16**:547, 1932.

7. Thomson, D. L., and Collip, J. B.: Physiol. Rev. **12**:309, 1932; Internat. Clin. **4**:102, 1933.

8. McJunkin, F. A.; Tweedy, W. R., and McNamara, E. W.: Am. J. Path. **13**:325, 1937.

function should be reflected in disturbance of the function and effects of the parathyroid glands.

On injection of parathyroid extract and in many cases of clinical hyperparathyroidism marked diuresis is a prominent effect. While this is usually associated with marked increase of calcium and phosphorus in the urine, it appears to be independent of these factors. Shelling, Kajdi and Guth [9] showed that the cause of death in acute overdosage with parathyroid extract was dehydration and loss of electrolytes as a result of the diuresis. Tweedy, Templeton and McJunkin [10] showed that many of the described effects on tissues of acute parathyroid overdosage are not found in bilaterally nephrectomized animals.

Hyperparathyroidism causes a reversal of the usual path of excretion of calcium from the body. In the normal person most excreted calcium is found in the feces and but a small amount in the urine. In the patient with hyperparathyroidism most of the calcium is excreted by way of the kidneys; in addition, the total of calcium excreted is increased.

These rather complex and not fully understood interrelationships between parathyroid function, kidney function and the metabolism of calcium and phosphorus give some help in clarifying relationships between hyperparathyroidism and renal disease, as will be discussed in succeeding sections.

EFFECT OF PRIMARY DECREASE OF RENAL FUNCTION ON THE PARATHYROIDS

A considerable mass of evidence has now accumulated indicating that renal insufficiency may give rise to parathyroid hyperplasia and hyperfunction. These observations are of considerable value in elucidating one phase of the parathyroid-kidney relationship; they suggest a mechanism of stimulation and function of the parathyroid glands.

Experimental Observations.—Significant experimental demonstration of the effect of renal damage on the parathyroids has been given by Pappenheimer and his associates.[11] They produced renal damage in rats by unilateral nephrectomy and partial destruction of the remaining kidney by thermocautery. This reduction in functional renal tissue led to a decided increase in the size of the parathyroids. The use of the thermocautery produced a nephritic lesion in the remaining kidney tissue, and the severity of these nephritic changes (and so, presumably, the

9. Shelling, D. H.; Kajdi, L., and Guth, L.: Endocrinology **22**:225, 1938.

10. Tweedy, W. R.; Templeton, R. D., and McJunkin, F. A.: (*a*) Am. J. Physiol. **115**:514, 1936; (*b*) Endocrinology **21**:55, 1937.

11. (*a*) Pappenheimer, A. M.: J. Exper. Med. **64**:965, 1936. (*b*) Pappenheimer, A. M., and Wilens, S. L.: Am. J. Path. **11**:73, 1935.

degree of deficiency of renal function) correlated with the degree of parathyroid enlargement. Bony lesions comparable to osteitis fibrosa cystica developed. The animals with decreased renal function were more sensitive to the injection of parathyroid extract, as measured by its effect on bone. That the parathyroid hyperfunction so induced may also, in turn, have its effect on the kidney has been revealed by the experiments of Donahue, Spingarn and Pappenheimer,[12] who found that the calcium content of the residual renal tissue was increased in proportion to the parathyroid enlargement. Removal of the parathyroids prevented this increase in renal calcium.

Pollack and Siegal[13] refer to a study by Hone on a syndrome occurring in dogs with renal insufficiency, characterized by osteoporosis of the skull, hyperplasia of the parathyroids and calcium deposits in soft tissues. They expressed the belief that this was a comparable disorder occurring in dogs.

Clinical Observations.—Virchow[14] noted metastatic calcification in cases of nephritis, and since that time the association of renal lesions and deposition of calcium has been frequently noted. Only recently, however, have the parathyroids been carefully examined in renal disease, and the reasons for the previously noted changes have become clearer. Bergstrand[15] noted in routine autopsies the frequency with which parathyroid enlargement accompanies renal damage and presented a study of 10 cases of renal disease associated with enlargement of the parathyroid glands. Vines[16] remarked on the occurrence of parathyroid hyperplasia in patients with chronic nephritis but did not give details. Box and de Wesselow[17] studied a patient with chronic nephritis whose blood calcium varied up to 20.1 mg. in 100 cc. and from clinical evidence suggested hyperparathyroidism. Lack of anatomic studies makes it difficult to determine the primary factor in this case.

Both Koopman[18] and Radnai[19] made histologic studies of the parathyroids in cases of chronic nephritis and failed to determine changes which they regarded as significant, though Radnai noted increased numbers of oxyphilic cells. Weights and measurements of the glands are not recorded. More recently, extensive detailed studies of the para-

12. Donahue, W.; Spingarn, C., and Pappenheimer, A. M.: J. Exper. Med. **66**:697, 1937.

13. Pollack, H., and Siegal, S.: J. Mt. Sinai Hosp. **2**:270, 1936.

14. Virchow, R.: Virchows Arch. f. path. Anat. **8**:103, 1855.

15. Bergstrand, H.: Acta med. Scandinav. **53**:644, 1921; **54**:539, 1921.

16. Vines, H. W. C.: The Parathyroids in Relation to Disease, London, Edward Arnold & Co., 1924.

17. Box, C. R., and de Wesselow, O. L. V.: Lancet **2**:543, 1925.

18. Koopman, H.: Frankfurt. Ztschr. f. Path. **25**:342, 1921.

19. Radnai, P.: Frankfurt. Ztschr. f. Path. **46**:97, 1933.

thyroids of patients with renal diseases have been made by Pappenheimer and Wilens,[11b] Castleman and Mallory [20] and Gilmour and Martin.[21] Also there have appeared a number of reports of single cases of renal disease in which parathyroid hyperplasia and effects of excessive function were outstanding.

Pappenheimer and Wilens [11b] published studies of 21 cases of chronic renal disease, using as controls 72 miscellaneous cases of other than renal conditions. The renal lesions in the 21 cases were of various types and accompanied by varied degrees of disturbance of renal function. The observers found an increase in the weight of the parathyroids roughly proportional to the severity and extent of the renal lesions and to the degree of clinical insufficiency. With severe lesions the increase in weight was over 100 per cent. The enlarged glands had a more compact cellular structure with a smaller proportion of adipose tissue, and the large water-clear type of cell appeared dominant.

Castleman and Mallory [20b] studied the parathyroids in 12 cases of chronic glomerular nephritis. In all but 2 of the cases there was gross enlargement of one or more glands. Microscopically, however, they found evidence of hyperplasia in all glands in every case. The fact that in some cases glands that were within normal limits of size showed satisfactory criteria of hyperplasia suggests that weights and measurements of parathyroids without skilled microscopic examination do not exclude the presence of hyperparathyroidism in a case of renal disease. It may be suggested, awaiting further study for proof or disproof, that in all cases of renal disease in which there is deficiency of function there is also some degree of overactivity of the parathyroid glands.

The same authors also describe 15 cases of assorted renal diseases other than glomerular nephritis in which there were mild degrees of parathyroid hyperplasia, although in 6 cases the glands showed no increase in size.

Gilmour and Martin [21] made extensive statistical studies of the weight of the parathyroid glands. They found definitely higher mean weights in cases of nephritis and other renal diseases than in other disease groups. They also noted that in the cases of renal disease the glands had a higher percentage of parenchyma per unit of weight. In 7 of 32 cases of the nephritis reported on, the weights of the parathyroid parenchyma were above the upper limit of normal which they had established. In a case of very long-standing chronic nephritis associated with widespread calcification in soft tissues and generalized osteitis fibrosa, the parathyroid tissue weighed 2,569 mg. In the first case they described, one of early

20. Castleman, B., and Mallory, T. B.: (*a*) Am. J. Path. **11**:1, 1935; (*b*) **13**:553, 1937.

21. Gilmour, J. R., and Martin, W. J.: J. Path. & Bact. **44**:431, 1937.

nephritis, there was great enlargement and hyperplasia of only one gland, while the other glands were normal in size and structure. It appears unlikely that the parathyroid change was secondary in this case. They also mentioned a case of nephritis in a late stage in which only three glands were found, but with weights exceeding the normal limit. In a group of 25 cases of renal disease other than nephritis they found 3 cases in which the weight of the parathyroid parenchyma exceeded normal. Two of these were cases of chronic pyelonephritis, and the third was a case of renal rickets.

Individual cases of hyperparathyroidism apparently initiated by renal insufficiency have been reported by Hubbard and Wentworth,[22] Barr and Bulger,[23] Albright,[2a,b] Kluge,[24] Pollack and Siegal,[13] Nelson [25] and Pons and Pappenheimer.[26] There is also the Cabot case.[27] Excluded from this number are cases of renal dwarfism and cases in which the parathyroid changes were limited to a single gland. Pons and Pappenheimer [26] in their tables gave some information regarding 2 other unpublished cases. Detailed descriptions of all these cases are easily available and will not be repeated here. The diversity of the actual lesions in the kidneys is noteworthy, however. Suppurative nephritis, subacute and chronic nephritis, arteriolosclerotic atrophy, polycystic disease and hydronephrosis have all been found to lead to parathyroid enlargement. In those cases in which the hyperparathyroidism was prominent clinically and easily diagnosed by the usual clinical criteria for hyperparathyroidism, the renal insufficiency was severe and had lasted over a long period with very slow progression. In some cases the classic lesions of osteitis fibrosa cystica resulted.

Fowweather and Pyrah [28] studied the blood calcium and inorganic phosphorus in 102 cases of various types of renal disease, and in about 50 per cent found the blood calcium to be over 11 mg. in 100 cc. Their results showed a tendency toward increase of blood calcium in widely different types of disease involving the kidneys. The changes in blood calcium and phosphorus generally associated with renal disease are a decrease in calcium and an increase in phosphorus. These changes, however, are not usually demonstrable until the renal disease is con-

22. Hubbard, R. S., and Wentworth, J. A.: Proc. Soc. Exper. Biol. & Med. **18**:307, 1920-1921.

23. Barr, D. P., and Bulger, H. A.: Am. J. M. Sc. **179**:449, 1930.

24. Kluge, E.: Virchows Arch. f. path. Anat. **298**:406, 1936.

25. Nelson, A. A.: Arch. Path. **24**:30, 1937.

26. Pons, J. A., and Pappenheimer, A. M.: Puerto Rico J. Pub. Health & Trop. Med. **13**:115, 1937.

27. Chronic Glomerular Nephritis; Secondary Parathyroid Hyperplasia, Cabot Case 22072, New England J. Med. **214**:320, 1936.

28. Fowweather, F. S., and Pyrah, L. N.: Proc. Roy. Soc. Med. **31**:593, 1938.

siderably advanced, and from the aforementioned results it may be that there is some stimulus in early renal disease which causes parathyroid hyperactivity, which in some cases more than counterbalances the tendency toward high phosphorus and low calcium.

Renal Dwarfism.—It is not intended to review here the subject of renal dwarfism (renal rickets). Various aspects have been reviewed by Mitchell and his collaborators,[29] Maddox,[30] Ellis and Evans,[31] Park and Eliot [32] and Price and Davie.[33] However, it has recently become evident that in many cases, and probably in all, the parathyroid glands play an essential role in the pathogenesis of the condition.

Although this condition is said to have been first described by Stenier and Neurenter [34] in 1870, it was not a clearly defined condition until the studies of Fletcher [35] appeared in 1911; it was further elucidated by Miller and Parsons,[36] Naish,[37] Barber,[38] Greene [39] and Parsons.[40]

Duken [41] suggested that there was an endocrine factor in renal rickets and pointed to the parathyroids as possibly involved. The involvement of the parathyroid glands in characteristic renal dwarfism was actually noted by Langmead and Orr [42] and by Smyth and Goldman.[43] Shelling and Remson,[44] Gilmour and Martin,[21] Price and Davie [33] and Howard [45] reported further instances in which studies of the parathyroid glands were made.

In the case reported by Langmead and Orr [42] death occurred at the age of 20, and four large parathyroids were found. The skeletal changes were consistent with hyperparathyroidism.

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29. (*a*) Mitchell, A. G.: Am. J. Dis. Child. **40**:101 and 345, 1930. (*b*) Mitchell, A. G., and Guest, G. M.: Ohio State M. J. **27**:134, 1931; J. Pediat. **3**:192, 1933.

30. Maddox, K.: M. J. Australia **1**:487, 1932.

31. Ellis, A., and Evans, H.: Quart. J. Med. **2**:231, 1933.

32. Park, E. A., and Eliot, M. M.: Renal Hyperparathyroidism with Osteoporosis (Osteitis) Fibrosa Cystica, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 29.

33. Price, N. L., and Davie, T. B.: Brit. J. Surg. **24**:548, 1937.

34. Stenier and Neurenter, cited by Howard.

35. Fletcher, H. M.: Proc. Roy. Soc. Med. **4**:95, 1911.

36. Miller, R., and Parsons, L. G.: Brit. J. Child. Dis. **9**:289, 1912.

37. Naish, A. E.: Brit. J. Child. Dis. **9**:337, 1912.

38. Barber, H.: (*a*) Lancet **1**:18, 1920; (*b*) Guy's Hosp. Rep. **71**:62, 1922; (*c*) **76**:307, 1926.

39. Greene, C. H.: Am. J. Dis. Child. **24**:1, 1922.

40. Parsons, L. G.: Arch. Dis. Childhood **2**:1 and 198, 1927.

41. Duken, J.: Ztschr. f. Kinderh. **46**:137, 1928.

42. Langmead, F. S., and Orr, J. W.: Arch. Dis. Childhood **8**:265, 1933.

43. Smyth, F. S., and Goldman, L.: Am. J. Dis. Child. **48**:596, 1934.

44. Shelling, D. H., and Remson, D.: Bull. Johns Hopkins Hosp. **57**:158, 1935.

45. Howard, T. L.: Am. J. Surg. **40**:323, 1938.

The case reported by Smyth and Goldman [43] was that of a boy aged 14, with a history of glomerular nephritis, marked impairment of renal function without hypertension, and generalized demineralization of bone. Autopsy showed five enlarged, diffusely hyperplastic parathyroid glands, composed mainly of chief cells with moderate numbers of oxyphilic cells. The urinary tract showed a hypertrophied, trabeculated bladder, bilateral hydroureter and hydronephrosis. Calcium deposition in kidney tissue was prominent, and calcium deposition was present in numerous other organs and tissues.

The report by Shelling and Remson [44] has certain distinctive features, in that an increased amount of parathyroid hormone was demonstrated in the blood prior to death by the hypercalcemia test of Hamilton and Schwartz.[46]

Price and Davie [33] reported a case:

A boy of 14 had suffered from thirst and polyuria since the age of 3 years. Deformities of the feet and legs were noted at 8 years and were progressive. Roentgenograms of the whole skeleton showed the characteristic changes of renal rickets. The urine was of low specific gravity, and the kidneys had no ability to concentrate it. Blood urea was 318 mg., serum calcium 13.6 mg. and serum phosphates 6.5 mg. in 100 cc. The boy appeared in comparatively good health, considering the degree of renal inadequacy, but there was rapid termination with uremia. Autopsy showed four enlarged parathyroid glands, measuring 10 by 6 by 4 mm., 15 by 6 by 4 mm., 15 by 8 by 6 mm. and 11 by 10 by 5 mm. (average normal size about 5 by 3 by 2 mm.). The changes found in the bones were essentially those of hyperparathyroidism. Microscopically, the parathyroid hyperplasia was uniform throughout and composed mainly of chief cells, but with a few oxyphils. The findings in the single kidney which was removed are particularly interesting. The kidney was very small and pale, with a diffusely granular surface and an adherent capsule. There was no evidence of pelvic dilatation or pyelitis. Microscopically there were seen many obliterated and partially obliterated glomeruli, but no evidence of active glomerular inflammation. Many tubules were greatly dilated, and some formed cysts. The main reaction was interstitial. The interstitial tissue was greatly increased in amount and showed infiltration with chronic inflammatory cells. There were numerous small foci of interstitial calcification, particularly within or immediately adjacent to basement membranes of tubules. No glomerular or intratubular calcification was noted. Just beneath the tubular basement membranes were small bodies which, the authors suggest, may have been calcium soaps. The vascular changes in the kidney were very slight.

Howard [45] likewise reported a case:

A 16 year old boy had shown deficient growth from birth. Bony deformities developed before school age. There was moderate frequency of urination with polyuria. The specific gravity of the urine was very low and fixed. The blood nonprotein nitrogen was 120 mg., the calcium 9.4 mg. and the phosphorus 11.3 mg. The nonprotein nitrogen in the blood rose to 300 mg. shortly before death. There was no hypertension. At autopsy three greatly enlarged parathyroid glands were

46. Hamilton, B., and Schwartz, C.: J. Pharmacol. & Exper. Therap. **46**: 285, 1932.

located, the largest measuring 15 mm. in maximal diameter. Microscopically, the glands all showed dense hyperplasia of chief cells. The skeletal changes were those of osteitis fibrosa. The kidneys were very small and microscopically were characterized by marked interstitial changes, with calcium deposits in and beneath the basement membranes of tubules, and by tubular dilatation, but showed no evidence of active glomerulitis or more than slight vascular changes.

A number of other cases presented a picture so closely resembling renal dwarfism and hyperparathyroidism that they have been reported by one observer as instances of the former condition and by another observer as instances of the latter. Thus the case reported by Davies-Colley [47] is reported by Bulger and his co-workers [48] as an instance of hyperparathyroidism and by Mitchell [29a] as an example of renal rickets, and Hutinel's [49] case, often cited as one of renal rickets, is mentioned by Shelling [50] as one of hyperparathyroidism. The cases of Cockayne and Lander [51] and Lightwood [52] are probably also examples of this condition.

An accurate evaluation of all the factors in the pathogenesis of renal dwarfism, with which all students of the subject are in agreement, has not yet been made, and for such an evaluation more data are required. Undoubtedly in many cases the initiating factor in the disease is a renal lesion. This renal lesion is often a congenital disturbance or obstruction, but various types of lesions have been noted. The essential character of the renal disease, however, is that it must develop before endochondral bone growth is completed and give rise to a severe degree of renal insufficiency which continues over a long period. The progressive nature of the usual type of nephritis does not allow it to meet these necessary conditions except in unusual cases, and this probably accounts for the comparative rarity of renal dwarfism as a complication of the nephritides of childhood.

From the facts that both clinical and experimental renal insufficiency produces parathyroid hyperplasia and hyperfunction and that parathyroid hyperplasia and hyperfunction have been demonstrated in a small number of cases of renal dwarfism, the evidence that the parathyroids play an essential role in this condition is very convincing. The lesions found in the bones are entirely comparable to those of osteitis fibrosa cystica, of renal hyperparathyroidism in adults and of experimental osteitis fibrosa produced by injections of parathyroid extract (Bodansky, Blair

47. Davies-Colley, J. N. C.: Brit. M. J. **1**:667, 1884.

48. Bulger, H. A.; Dixon, H. H.; Barr, D. P., and Schregardus, O.: J. Clin. Investigation **9**:143, 1930.

49. Hutinel, V.: Gaz. d. hôp. **80**:27, 1912.

50. Shelling, D. H.: The Parathyroids in Health and in Disease, St. Louis, C. V. Mosby Company, 1935.

51. Cockayne, E. A., and Lander, F. P. L.: Arch. Dis. Childhood **7**:321, 1932.

52. Lightwood, R.: Arch. Dis. Childhood **7**:193, 1932.

and Jaffe;[53] Bodansky and Jaffe[54]), though modified by an effect on bones undergoing endochondral ossification, which gives rise to the stunting of longitudinal growth. This sequence in the development of renal dwarfism is backed by the experimental work of Pappenheimer,[11a] who produced a comparable condition in young rats by producing renal insufficiency and keeping them on a deficient calcium intake. If the diet contained sufficient calcium and phosphorus, the parathyroid hyperplasia was only exceptionally accompanied by osteofibrotic skeletal changes. On a very low calcium intake the skeletal lesions were similar to those of marked rickets, whereas with a moderately deficient calcium intake the skeletal lesion was osteitis fibrosa. Thompson[55] prepared an extract of the parathyroid glands, which he noted would retard and limit growth in rats. Jaffe and Bodansky[56] noted that dogs treated by injections of parathyroid extract for long periods were stunted. Shelling, Asher and Jackson[57] reported moderate retardation of growth of rats receiving daily injections of parathyroid extract. It thus appears that renal dwarfism is but a modification of the renal hyperparathyroidism that occurs in adults, a modification in which the disease is of such severity and chronicity as to produce skeletal lesions. With this conclusion Park and Eliot[32] are in complete agreement, and in their excellent review they have convincingly outlined the pathogenesis of this condition. The evidence for other factors in many of the cases cannot, however, be overlooked, and the presence of infantilism and other endocrine disturbances in some cases is not so easily explained on this basis. Several authors (Chown;[58] Roberts;[59] Chown and Lee[58d]) have suggested that the pituitary gland may be involved. Evidence that this gland may play a part in stimulation of the parathyroids has been produced by Houssay,[60] Hoffman and Anselmino,[61] Hertz and Kranes[62] and others.

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53. Bodansky, A.; Blair, J. E., and Jaffe, H. L.: J. Biol. Chem. **88**:629, 1930.

54. Bodansky, A., and Jaffe, H. L.: J. Biol. Chem. **93**:543, 1931; J. Exper. Med. **53**:591, 1931.

55. Thompson, J. H.: J. Physiol. **70**:xli, 1930.

56. Jaffe, H. L., and Bodansky, A.: J. Exper. Med. **52**:669, 1930.

57. Shelling, D. H.; Asher, D. E., and Jackson, D. A.: Bull. Johns Hopkins Hosp. **53**:348, 1933.

58. (*a*) Chown, B.: Canad. M. A. J. **35**:134, 1936; (*b*) Brit. J. Surg. **23**:552, 1936; (*c*) Canad. M. A. J. **37**:16, 1937. (*d*) Chown, B., and Lee, M.: Am. J. Dis. Child. **53**:117, 1937. (*e*) Chown, B.; Lee, M., and Teal, J.: Canad. M. A. J. **35**:513, 1936; **36**:7, 1937.

59. Roberts, J. F.: Ann. Int. Med. **9**:1729, 1936.

60. Houssay, B. A.: Certain Relations Between Parathyroids, Hypophysis and Pancreas, in Harvey Lectures, 1934-1935, Baltimore, Williams & Wilkins Company, 1936, p. 116.

61. Hoffman, F., and Anselmino, K. J.: Klin. Wchnschr. **13**:44, 1934.

62. Hertz, S., and Kranes, A.: Endocrinology **18**:350, 1934.

Mitchell [29a] attributed the lesions in the skeleton to a deficiency in calcium absorbed from the intestine. He suggested that in the presence of renal insufficiency the intestinal mucosa may excrete waste endogenous phosphates, instead of the kidneys, the phosphorus forming with ingested calcium insoluble calcium phosphate, thus preventing absorption. Albright [2c] also did not agree that the parathyroids have a direct effect in the release of calcium from the bones and the production of skeletal lesions. The reasons he gave for believing that the hormone does not act on bone tissue are as follows. 1. The bones are not abnormal in hypoparathyroidism. 2. Primary hyperparathyroidism may exist without evidence of bone changes. 3. Bone changes in hyperparathyroidism can be made to regress by means of diet alone. On the other hand, convincing evidence has been produced indicating an effect of parathyroid extract directly on bones, even in the absence of the kidneys. Jaffe,[63] Thomson and Collip,[7] Selye [6] and McJunkin and his associates [8] found a definite reaction in bony tissue following injection of parathyroid extract. While such details of the mechanism may be in dispute, the evidence that hyperparathyroidism is an essential part of renal dwarfism appears overwhelming. Park and Eliot [32] made the suggestion that in these cases the disease should be termed renal hyperparathyroidism with osteitis fibrosa cystica. This term defines the underlying condition, indicates the pathogenesis of the disease and describes the condition in the bones (albeit inaccurately). Its general adoption would relieve the confusion attending the term "renal rickets" and identify the condition with its counterpart in adults.

Both Shelling [50] and Park and Eliot [32] emphasized that it may be very difficult in individual cases to distinguish renal hyperparathyroidism from primary or idiopathic hyperparathyroidism, particularly in the terminal stages, when the two may be identical. Shelling [50] puts great emphasis on the history of renal symptoms antedating evidence of changes in the skeleton. This would not appear to be always reliable. In MacCallum's [1] case the nephritis was primary as regards the time at which it became evident, yet the parathyroids showed a single adenoma rather than diffuse hyperplasia. Albright, Drake and Sulkowitch [21] pointed out that in many cases of primary hyperparathyroidism (with a parathyroid adenoma) renal symptoms may appear before bone symptoms or roentgen evidence of skeletal disease and that one should not wait for bone symptoms to make a diagnosis of hyperparathyroidism. They favored a high level of serum calcium as being of value in suggesting primary hyperparathyroidism as opposed to a disease in which renal insufficiency is the first step. The presence of calcium deposits in the kidney or of renal calculi is not, as Shelling [50] suggested, a distinguishing

63. Jaffe, H. L.: Arch. Path. **16**:63 and 236, 1933.

characteristic of primary hyperparathyroidism alone, for these findings are not infrequent in cases of renal rickets. Again experimental work has been done which confirms these findings. Donahue, Spingarn and Pappenheimer [12] found increased calcium content in the remaining portions of damaged kidneys in rats in the presence of hyperplastic parathyroids. That this was due to parathyroid action was shown by the absence of this increase in renal calcium when the parathyroids were removed.

The actual lesions in the genitourinary tract in renal rickets divide themselves into two groups. In one group there are lesions of a congenital nature, either a cystic disorder of the kidneys or some abnormality of the lower part of the urinary tract resulting in dilatation of the ureters and hydronephrosis. In the other group are those peculiar changes of the kidney which commonly have been called chronic interstitial nephritis. Here there is advanced glomerular destruction and gross tubular dilatation, but evidences of antecedent glomerulonephritis, such as thickened and adherent tufts or crescents in Bowman's capsules, are absent, as are usually, also, vascular changes, hypertension and cardiac hypertrophy. Instead there are progressive inflammation and fibrosis in interstitial tissues, with deposition of small amounts of calcium. This group is entirely analogous to that produced as a result of primary chronic hyperparathyroidism.

As has been stated by Price and Davie,[33] these findings suggest the possibility that the syndrome of renal rickets may have its beginnings either in the endocrine system (parathyroids or hypophysis) or in the genitourinary system. In either case the parathyroids play an essential part, and the end picture may be clinically the same. Distinction as to the origin may then be possible only by (1) evidence of a primary parathyroid origin from the presence of a single parathyroid tumor or (2) evidence of a primary renal origin from the presence of a congenital abnormality of the kidneys or of the urinary tract. Such a theory of multiple origins of renal rickets does much to explain certain findings which were difficult to fit into the picture on the basis of a purely endocrine origin.

Comment.—The change in the glands in renal hyperparathyroidism appear to be true hyperplasia, affecting all the glands in the same fashion, though not necessarily producing the same degree of enlargement in each gland. The increase in size of the glands may be truly enormous; in one case a single gland weighed nearly 5 Gm. (normal about 60 mg.). The size is mainly accounted for by true hyperplasia. The individual cells are not increased in size and are usually reported to be mainly of the small chief cell type, densely packed together, with decrease in the proportion of fat cells to parenchyma. The details of these changes

have been carefully studied and clearly described by Castleman and Mallory.[20b] The epithelial cells are arranged in wider columns or in solid masses of cells without discernible columnar arrangement. In more advanced cases there may be a tendency toward acinar arrangement. There are no mitoses. Oxyphile cells are more numerous. The microscopic appearance is diffuse and uniform throughout all the glands, though the glands may show variable degrees of increase in size. In the gross the glands are a creamy gray color, rather than light brown, and are firm in consistence.

That the parathyroid hyperplasia of renal disease is actually accompanied by increase in the amount of parathyroid hormone in the blood has been ably demonstrated by Highman and Hamilton,[64] using the hypercalcemia test in rabbits as devised by Hamilton and Schwartz [46] and Hamilton and Highman.[65] While Highman and Hamilton [64] did not find a strict proportionality between the rise of inorganic phosphorus in the blood and the increase in hormone, they suggested that the hyperphosphatemia was probably the stimulating factor.

The actual mechanism by which renal insufficiency brings about parathyroid hyperplasia will not be discussed in detail, as sufficient experimental work has not been performed to enable one to reach an unassailable conclusion. Parenteral administration of phosphates has produced parathyroid hyperplasia in rabbits (Drake and others [66]), and several authors agree that retention of phosphates is the probable mechanism. Numerous experiments have indicated that the first effect of injection of parathyroid extract is to produce phosphate diuresis, and the hormone evidently has a direct effect on the kidney, lowering the threshold for phosphorus. Albright [2n] has recently suggested low blood calcium as the stimulus for parathyroid hyperplasia. Park and Eliot [32] suggested that it is change in the calcium and inorganic phosphorous equilibrium of the blood which acts as a stimulus to parathyroid action. Acidosis may also be suggested as a possible stimulus to parathyroid hyperplasia. Solution of this problem awaits further investigation.

PRIMARY HYPERPARATHYROIDISM AND ITS EFFECT ON THE KIDNEYS

The Parathyroid Lesion.—Castleman and Mallory [20] and Albright and others [2k, n] stressed the fact that two types of primary hyperparathyroidism (as far as is known) may occur, either of which may produce osteitis fibrosa and frequently renal disease. These types may be distinguished

64. Highman, W. J., Jr., and Hamilton, B.: J. Clin. Investigation **16**:103, 1937; Arch. Path. **26**:1029, 1938.

65. Hamilton, B., and Highman, W. J., Jr.: J. Clin. Investigation **15**:99, 1936.

66. Drake, T. G.; Albright, F., and Castleman, B.: J. Clin. Investigation **16**: 203, 1937.

by the morphologic aspects of the parathyroid glands, but the effects produced elsewhere (skeleton, kidneys) may be identical. The commoner type is characterized by an adenomatous enlargement of a single gland. In the other type there is a comparatively uniform increase in size of all four glands, as well as a distinctive microscopic appearance.

The adenomatous enlargement of a single gland has been described in detail by Castleman and Mallory [20a] and by Hunter and Turnbull.[67] Such enlargement may be truly enormous. Sometimes it affects only part of a gland, leaving around it a rim of normal parathyroid tissue. In the majority of cases the growth is composed of types of chief cells; in a few it is composed of *wasserhelle* cells (Elsom, Wood and Ravdin [68]); rarely, oxyphile adenoma, which apparently is hyperfunctioning, has been reported (Chown; [58a,b,c] Venables; [69] Warren and Morgan [70]).

Turnbull [67] expressed the opinion that the adenomatous enlargements were not autonomous new growths but enlargements due to functional hyperactivity. He compares this with the occurrence of localized areas of overactivity in the thyroid. Castleman and Mallory,[20] however, consider that these localized parathyroid enlargements represent neoplasia, basing this belief mainly on the localized character of the proliferative process.

The diffuse type of enlargement of the parathyroid glands in "primary" hyperparathyroidism is characterized by the presence of large *wasserhelle* cells making up the whole of the tissue, to the exclusion of other types of cells which are normally found in the glands. Albright and his associates [2k, n] have made the most complete studies on this type of hyperparathyroidism. They believe this *wasserhelle* type of enlargement is secondary to some unknown stimulus. The glands may have a weight thirty to one hundred times normal. This increase in size can be explained mainly by hypertrophy of the cells, with little or no increase in number. The appearance is similar in all the glands. The cells are very large, with clear watery cytoplasm. There is increased tendency to glandular arrangement. Oxyphile cells, chief cells and mitoses are absent. Fat tissue is also absent. No case has been found in which the condition has been present in mild or transition forms, or in only a portion of a gland. Once the condition is present, it remains indefinitely, but there is little tendency to regeneration if a portion is removed at operation. The weight of the gland tissue and the degree of hyperparathyroidism appear to be definitely correlated.

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67. Hunter, D., and Turnbull, H. M.: Brit. J. Surg. **19**:203, 1931.

68. Elsom, K. A.; Wood, F. C., and Ravdin, I. S.: Am. J. M. Sc. **191**:49, 1936.

69. Venables, J. F.: Guy's Hosp. Rep. **83**:194, 1933.

70. Warren, S., and Morgan, J. R. E.: Arch. Path. **20**:823, 1935.

The Renal Lesion.—Primary hyperparathyroidism associated with marked renal insufficiency has been reported by Elsom, Wood and Ravdin,[68] Baker and Howard,[71] Bellin and Gershwin,[72] Albright,[2] Anderson [73] and others.

Elsom, Wood and Ravdin [68] noted that the renal disease associated with primary hyperparathyroidism has certain features which distinguish it from the usual types of chronic nephritis. Hypertension, cardiac enlargement, edema and retinal exudates are usually absent or very inconspicuous. In many cases the subject appears to tolerate an unusual degree of kidney damage and insufficiency without much subjective discomfort. It seems possible to relate these distinctive clinical features to the morphologic peculiarities of the renal lesion. Vascular lesions are characteristically absent or slight, as is active glomerular involvement. Morphologically one would expect the greatest interference with tubular function, and this seems to be reflected in the inability to produce concentrated urine. Correction of the hyperparathyroidism might be expected to halt the progression of the lesion (Baker and Howard;[71] Bellin and Gershwin [72]), but improvement in renal function could occur only in early cases (Baker and Howard [71]).

The literature now contains many reports of cases of primary hyperparathyroidism. In a large proportion of the reported cases there was some evidence of disturbance of renal function or of the presence of renal calculi. Polyuria and polydipsia, associated usually but not necessarily with hypercalciuria, were among the earliest and most constant of symptoms. In later stages it was extremely common to find a slight amount of albumin and a few casts in the urine, with lowering and fixation of the specific gravity. Treatment in early stages sometimes produced improvement in renal function and ability to concentrate (Baker and Howard;[71] Cooley;[74] Pemberton and Geddie;[75] Boyd, Milgram and Stearns,[76] and others). The presence of renal calculi, with associated obstruction and infection, may change the usual renal picture.

In some cases the evidence of renal disease overshadowed other evidences of hyperparathyroidism, and in recent years, since involvement of the kidneys has been more generally realized to be an occurrence in hyperparathyroidism, such cases have been reported more frequently.

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71. Baker, B. M., Jr., and Howard, J. E.: Bull. Johns Hopkins Hosp. **59**: 251, 1936.

72. Bellin, D. E., and Gershwin, B. S.: Am. J. M. Sc. **190**:519, 1935.

73. Anderson, W. A. D.: Endocrinology **24**:122, 1939; J. Pediat., to be published.

74. Cooley, T. B.: Am. J. Dis. Child. **42**:691, 1931.

75. Pemberton, J. de J., and Geddie, K. B.: Ann. Surg. **92**:202, 1930.

76. Boyd, J. D.; Milgram, J. E., and Stearns, G.: J. A. M. A. **93**:684, 1929.

In the older literature on hyperparathyroidism renal changes were described occasionally, but careful histologic studies of the kidneys in cases of hyperparathyroidism rarely have been made.

Calcium precipitations in the form of renal calculi or parenchymal deposits or both occur with great regularity. Randall's [77] studies indicate that a parenchymal calcium deposit is the primary lesion in the cases in which renal calculi are found. Askanazy [78] in his case noted contracted kidneys with interstitial inflammation and many areas of calcification and interstitial inflammation. Molineus [79] described contracted kidneys in 2 cases. Harbitz [80] found interstitial inflammation and calcareous concretions of phosphates and carbonates. Marked calcium deposits were found by Hartwich,[81] Parreira and Castro-Freire,[82] Wanke, [83] Ask-Upmark,[84] Noble,[85] Peneche,[86] Hoffheinz [87] and MacCallum.[1]

Knowledge of renal disease in association with hyperparathyroidism was summarized in 1934 by Albright and co-workers.[2j] They described the renal lesions as being of three types. Stone formation, which they found to be the most commonly mentioned renal complication, they designated as type I. However, as stated in a foregoing paragraph, deposition of calcium in the parenchyma is probably primary, and so must be even more frequent than calculus formation, though less apt to be noticed, unless the deposit is so severe as to show in a roentgenogram or to be striking at postmortem examination.

This parenchymal calcium deposition, which they termed nephrocalcinosis, they designated as type II, stressing the occurrence of calcium deposits in the renal tubules and the presence in the urine of granular, calcium-containing casts. The extratubular mineral deposits, which are even more striking and important, are neglected by them. They suggested that the deposition of calcium in the kidney causes permanent and serious damage of the kidney, with chronic inflammatory changes and subsequent

77. (*a*) Randall, A.: Surg., Gynec. & Obst. **64**:201, 1937; (*b*) Ann. Surg. **105**:1009, 1937. (*c*) Randall, A.; Eiman, J. E., and Leberman, P. R.: J. A. M. A. **109**:1698, 1937.

78. Askanazy, M.: Arb. a. d. Geb. d. path. Anat. Inst. zu Tübingen **4**:398, 1904.

79. Molineus: Arch. f. klin. Chir. **101**:333, 1913.

80. Harbitz, F. J.: J. M. Research **32**:361, 1915.

81. Hartwich, A.: Virchows Arch. f. path. Anat. **236**:61, 1922.

82. Parreira, H., and Castro-Freire, L.: Compt. rend. Soc. de biol. **95**:1590, 1926.

83. Wanke, R.: Beitr. z. klin. Chir. **136**:664, 1926.

84. Ask-Upmark, E.: Acta med. Scandinav. **74**:284, 1930; Acta chir. Scandinav. **68**:551, 1931.

85. Noble, T. P.: J. Bone & Joint Surg. **14**:181, 1932.

86. Peneche, R.: Zentralbl. f. allg. Path. u. path. Anat. **37**:535, 1926.

87. Hoffheinz, S.: Virchows Arch. f. path. Anat. **256**:705, 1925.

sclerosis and contraction, the end point simulating chronic nephritis. With this conclusion other pathologists agree (Chown [58a]) and disagree (Pappenheimer and Wilens [11b]).

In type III, which they call "parathyroid poisoning," deposits of calcium occur in the kidney but, in addition, in various other organs, such as the lung, stomach and heart.

It is evident that in these three types the primary or essential factor as far as the kidneys are concerned is the deposition of calcium in the renal parenchyma, and thus division into types is only a clinical convenience. From the pathologic standpoint the important problem seems to be whether or not deposition of calcium per se damages kidney tissue to such an extent that renal function may be decreased.

It seems significant that almost constantly in cases of hyperparathyroidism in which histologic studies were carefully made a particular type of lesion has been described. This renal change is predominantly interstitial. There is interstitial infiltration by chronic inflammatory cells, interstitial fibrosis and interstitial deposition of calcium, particularly in or adjacent to tubular basement membranes. Tubular and intratubular calcium deposits, while usually present, are less prominent, particularly in late stages, and seem to be more characteristic of an acute phase. Frequently tubules are dilated and lined by flattened epithelium. Often small cysts are formed. Glomeruli are partially or completely fibrosed, but evidence of proliferative or exudative changes in glomeruli, such as are seen in glomerular nephritis, are absent. Vascular involvement is usually slight; when present, it appears to be an unrelated change.

Many of the calcium deposits, both those within tubules, associated with desquamation and destruction of tubular epithelium, and peritubular masses, may give rise to obstruction of the tubule and an effect on other portions of the nephron. The tubular dilatations and many of the obliterations of glomerular tufts are expressions of these obstructive effects. Other conditions in which tubular obstruction is productive of renal damage have been described by Forbus and his associates [88] in Bence Jones proteinuria and by Duguid [89b] in lesions produced by calciferol and described in more detail elsewhere. It is obvious that widespread obstruction of tubules may severely damage the kidney and produce insufficiency. MacNider [90] described regeneration of tubular epithelial cells in a more resistant form after injury by uranium nitrate and mercury bichloride. No studies have been made which indicate whether or not such regeneration of tubular cells, with acquired resis-

88. Forbus, W. D.; Perlzweig, W. A.; Parfentjev, I. A., and Burwell, J. C., Jr.: Bull. Johns Hopkins Hosp. **57**:47, 1935.

89. Duguid, J. B.: (*a*) Lancet **2**:983, 1930; (*b*) **2**:987, 1938.

90. MacNider, W. de B.: Ann. Int. Med. **12**:147, 1938.

tance, may follow slighter degrees of damage by hyperparathyroidism. Such a process, however, may partially explain the immunity acquired by many experimental animals to injections of parathyroid extract.

Some of the interstitial calcium deposits may have been primarily in tubules and, following degeneration of the injured nephron, appear to be in interstitial tissue surrounded by more prominent fibrous tissue.

Parenchymal calculi may be formed by coalescence of calcium concretions or by ulceration of the tubular epithelium overlying a protruding peritubular mineral deposit, and subsequent precipitation from tubular urine. The development of calculi, with obstruction and infection, may modify the picture of the renal lesion.

Experimental Results.—Experimental work with parathyroid extract would naturally be looked to for the solution of the pathogenesis of the renal lesions in hyperparathyroidism. The results are somewhat disappointing. Most experimenters (Hueper;[91] Learner;[92] Cantarow, Stewart and Housel[93]) produced acute hyperparathyroidism by large doses, a condition that does not simulate the relatively mild chronic hyperparathyroidism seen in man. Many animals seem to have or to develop tolerance toward the extract. Selye[6] showed that in rats this apparent immunity which develops is really a change in the response of the tissues affected, in such a fashion that an osteoblastic rather than an osteoclastic action may be produced in bones. Whether or not there develops a change in the response of the kidney to continued administration of the parathyroid extract has not been demonstrated.

Hueper,[91] Learner[92] and Cantarow, Stewart and Housel[93] described the renal changes in dogs in experimental acute hyperparathyroidism. Their findings in the kidney are all essentially similar. Marked degenerative changes were found in the renal tubular epithelium. All portions of the cortical tubules were involved, and occasionally the collecting tubules to a lesser degree. Dilated tubules, some lined by flattened epithelium, were frequent. The amount of calcium deposited did not parallel the value of serum calcium. The mineral deposits were found in tubular epithelium and as casts in the tubular lumen. Hueper[91] also described some calcification of tubular basement membranes and of Bowman's capsule.

McJunkin and his co-workers[94] and Cantarow and his associates[93] were emphatic that the calcification in experimental hyperparathyroidism is not metastatic in the sense that calcium is deposited in tissue otherwise

91. Hueper, W. C.: Arch. Path. **3**:14, 1927.

92. Learner, A.: J. Lab. & Clin. Med. **14**:921, 1929.

93. Cantarow, A.; Stewart, H. L., and Housel, E. L.: Endocrinology **22**:13, 1938.

94. McJunkin, F. A.; Tweedy, W. R., and Breuhaus, H. C.: Arch. Path. **14**: 649, 1932.

normal. Cantarow and his associates [93] invariably found regressive changes in the kidneys, which they believed contributed to the localization of the deposits. McJunkin and his associates [94] suggested that this injury was produced by disturbance of the calcium components of the tissue fluids of the cells themselves.

The most enlightening experimental studies are those of Chown, Lee and Teal.[58e] They used young rats, giving them graduated parenteral doses of parathyroid extract over long periods. Early lesions consisted of intratubular calcium deposits, coarse and fine interstitial calcium deposits and extension of calcium masses into the tubular lumens, with a leukocytic reaction. Many of these deposits were only temporary. Late results (up to one hundred and seventy-four days) were very striking, with cystic tubular dilatation, occasionally irregular pelvic dilatation and chronic focal inflammatory reaction. Varying amounts of interstitial reaction and proliferation occurred, with some glomerular changes. Calcium deposits in glomeruli were not seen. Eventually, in late cases, calcium deposition was often small in amount and was present only in interstitial tissues. The resemblance of this to the findings in the kidneys in clinical cases of renal rickets and primary hyperparathyroidism is evident.

It seems from the evidence only fair to conclude that hyperparathyroidism may produce definite kidney disease. To decide whether this renal damage may be produced as a result of hypercalcemia per se or only with the addition of other factors is more difficult. Considerable evidence indicates that in hyperparathyroidism there are other assisting elements. Definite evidence of degenerative changes in the kidney in experimental acute hyperparathyroidism has been referred to in a foregoing paragraph. This is reflected in the common finding in patients with parathyroid adenoma of a loss of concentrating power by the kidneys, with a fixed low specific gravity of the urine, which may be relieved if the adenoma is surgically removed in early stages of the disease. That hypercalcemia alone may not be very injurious is indicated in the report by Reed [95] of a young adult human subject who maintained "hypercalcemia of 24 mg. for 8 days by vitamin D overdosage without evidence of toxicity or subsequent damage." Duguid [89b] in experimental work with rats given acid sodium phosphate and calciferol found that what begins as a purely tubular degenerative lesion, with calcification, may eventually produce in the kidney microscopic changes very difficult to distinguish from an advanced stage of chronic glomerulonephritis. The primary change was a tubular degenerative change with focal calcification. Groups of degenerated convoluted tubules of the cortex either atrophied and left areas of fibrosis or became dilated and cystlike. The glomeruli in their turn degenerated, the capillaries becoming hyaline and

95. Reed, C. I.: J. A. M. A. **102**:1745, 1934.

their lumens obliterated, so that eventually the glomerular tufts were transformed into solid masses of hyaline substance, which later became fibrosed. These glomerular lesions were found only in the more severely affected animals which survived some months after the production of the initial lesion. The variety of histologic pictures produced often imitated the various forms of primary chronic nephritis in man.

Renal Calcification.—Because of the stress which has been put on the deposition of calcium in the kidney in the renal lesion of primary hyperparathyroidism, certain points about renal calcification will be reviewed. There is no doubt that in experimental acute hyperparathyroidism disturbance of renal function having no relation to deposition of calcium occurs, even though in such experiments extensive calcium masses may be laid down in the kidney in less than forty-eight hours. The anuria which regularly precedes death in acute hyperparathyroidism appears, however, to be related to loss of electrolytes, and the symptoms may be relieved by replacement of the deficient water and electrolytes. However, in the chronic forms of hyperparathyroidism the deposition of calcium appears to be a definite factor leading to damage of the kidney tissue and decreased efficiency of renal function, as well as to formation of calculi and resulting obstruction and infection.

The subject of pathologic calcification was reviewed by Barr.[96] He emphasized the rarity of calcium metastases in human diseases, and also the frequency with which they have been found related to nephritis. He stated that it is difficult to find a case of extensive metastatic calcification in which a renal element can be definitely excluded.

Factors of importance in the precipitation of calcium include the concentration of calcium, the concentration of phosphates and the degree of alkalinity of the serum and tissue fluids. Localized increase in alkalinity may cause deposition of calcium even without great increase in concentration of calcium and phosphates. If there is increase in concentration of calcium and (or) phosphates, as there may be in hyperparathyroidism, local relative alkalinity may still be a factor causing precipitation of calcium in a particular place. On this basis has been explained the frequency of calcium deposits in the lungs, stomach and kidneys. Kleinmann[97] emphasized that degenerating and devitalized tissues similarly have relative alkalinity.

Wells, Holmes and Henry[98] pointed out the peculiarity of the calcium deposits in the kidney when the tubules are the structures involved. Tubular calcification they compare to calcification of organic material

96. Barr, D. P.: Physiol. Rev. **12**:593, 1932.

97. Kleinmann, H.: Virchows Arch. f. path. Anat. **268**:686, 1928; Biochem. Ztschr. **196**:98, 146 and 161, 1928.

98. Wells, H. G.; Holmes, H. F., and Henry, G. R.: Am. J. M. Research **25**: 373, 1911-1912.

in the urine rather than to calcification of tissues with lime salts directly from the blood. The epithelium and tube cast deposits they found to contain calcium only as phosphate, whereas in interstitial tissues carbonate could be demonstrated as well, the calcium in the latter situation probably coming from the blood. In the urine calcium is present chiefly in the form of the acid phosphate. The common stain used to demonstrate the presence of calcium in tissues is silver nitrate. Wells and his co-workers [98] stated, and the statement has been fully confirmed by the work of Cameron,[99] that silver nitrate has no affinity for calcium and detects not calcium but certain acid radicals, particularly the phosphate.

Experimental and metabolic studies have indicated that increased calcium and phosphorus in the urine, as well as degenerative changes in kidney tissue, are characteristic features of hyperparathyroidism. Thus in acute phases of hyperparathyroidism, particularly, conditions are ripe for the deposition of calcium in renal tubules. The experiments of Chown [58a,c,e] have shown that with progression of the renal lesion much of this tubular deposit is removed. Adequate studies of the amount of epithelial regeneration which may follow have not been made, but evidence indicates that even up to this stage there may be return of the kidney to more efficient function. In the later stages of the renal lesion, when chronic insufficiency of renal function is present, the deposition of calcium is predominantly interstitial. The extent of this interstitial accumulation of calcium is probably not realized because of the use of the common but inadequate silver nitrate method for the demonstration of calcium, which, as was emphasized in a foregoing paragraph, stains not the calcium but the phosphate radical. Extensive interstitial calcium deposits of this sort are a rare occurrence in any condition other than hyperparathyroidism. Experimentally induced hypervitaminosis D may produce a somewhat similar renal condition in an acute phase, as will be discussed separately. The extensive renal calcification sometimes accompanying high intestinal obstruction (Cooke;[100] Brown and co-workers [101]) is mainly tubular and dependent on dystrophic changes in tubular epithelium.

The part played by renal phosphatase in renal calcification has not been thoroughly investigated. Hyperparathyroidism with skeletal lesions is associated with increased serum phosphatase, but the phosphatase of the kidney tissue under these circumstances is not known. The work of Rosenheim and Robison [102] suggested that renal phosphatase is a

99. Cameron, G. R.: J. Path. & Bact. **33**:929, 1930.

100. Cooke, A. M.: Quart. J. Med. **2**:539, 1933.

101. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Arch. Int. Med. **32**:425, 1923.

102. Rosenheim, A. H., and Robison, R.: Biochem. J. **28**:712, 1934.

factor of some importance for calcification in vitro. One might expect, though as yet without concrete evidence, that in hyperparathyroidism increase of phosphatase in kidney tissue would be an important factor causing the unusual type of renal calcification.

Renal Lithiasis.—The presence of renal calculi has been noted very frequently in cases of hyperparathyroidism. Among 75 cases in which parathyroid adenoma was proved to be present, collected by Compere,[103] there were 24 in which renal calculi were found. In the series of 32 cases of hyperparathyroidism reported by Hunter,[104] calculi were found in 10, or about the same proportion. Barney and Mintz [105] noted that of 65 cases of parathyroidism reported by various authors, stones were present in 15. In the series of cases reported by Barney and Mintz [106] from Boston almost 70 per cent showed renal stones, a much higher percentage than in the other collected instances that have been noted here. Albright and his associates [2j] mentioned calculous disease as the commonest renal complication of hyperparathyroidism in their cases.

It is evident then that renal formation of stones is one of the commonest results of hyperparathyroidism. Estimations as to the importance of the parathyroids in the general problem of the renal formation of stones have been variable. Barney and Mintz [105] stated that hyperparathyroidism was a factor in 10 per cent of cases of renal calculi, but later they [106] revised this figure to between 4 and 5 per cent. This figure was based on a series of 340 patients with urinary lithiasis, some of whom were proved by operation to be suffering from hyperthyroidism. In other clinics the proportion has been found to be much lower. Griffin, Osterberg and Braasch [107] found hyperparathyroidism to be a factor in less than 0.2 per cent of 1,206 cases of urinary lithiasis. Geographic location, a known factor of importance in calculous disease, would cause slight variation in such figures but hardly enough to account for such a discrepancy. Marquardt [108] in a small series of cases did not find hyperparathyroidism to be a factor. Fowweather and Pyrah [28] also agreed that primary hyperparathyroidism is a factor in only a very small proportion of cases of renal calculi.

Renal calculi are not common in children but have been noted in many who had renal dwarfism (Davies-Colley [47]; Barber [38b]; Parsons [40]; Mitchell [29]) which, as has been indicated, is associated with hyperpara-

103. Compere, E. L.: Arch. Surg. **32**:232, 1936.

104. Hunter, D.: Lancet **1**:897 and 946, 1930; Quart. J. Med. **24**:393, 1931; Brit. M. J. **1**:982 and 929, 1937.

105. Barney, J. D., and Mintz, E. R.: J. A. M. A. **103**:741, 1934.

106. Barney, J. D., and Mintz, E. R.: J. Urol. **36**:159, 1936; Brit. J. Urol. **8**: 36, 1936.

107. Griffin, M.; Osterberg, A. E., and Braasch, W. F.: J. A. M. A. **111**:683, 1938.

108. Marquardt, C. R.: Wisconsin M. J. **36**:177, 1937.

thyroidism and frequently with calcium deposits in the kidneys. The probable mechanism by which renal calculi are formed in hyperparathyroidism has been revealed in the studies made by Randall [77] and by Chown, Lee and Teal.[58e] Randall showed that the basic lesion in renal stone formation is a parenchymal deposit of calcium in the kidney substance, particularly in the walls and intertubular spaces of the renal papilla. These plaquelike calcium masses may lose their epithelial covering and be subjected to constant contact with calycine urine, acting then as a nidus on which further deposition may occur and being held in place until a stone of some size is formed. The association of these conditions with evidence of tubular damage has also been emphasized by Randall.

From the earlier discussion of the morphologic changes in the kidney, it is seen how frequently hyperparathyroidism produces just such an initiating lesion for the formation of stone. Tubular damage and interstitial calcium deposits are marked features. While the deposition of calcium is usually most prominent in the cortex, there is also frequent and sometimes severe involvement of the papillae. Randall and co-workers [77c] described production of the characteristic lesion in a papilla by administration of parathyroid extract to a dog.

The experimental work of Chown, Lee and Teal [58e] showed how the small calculi within kidney tissue may be formed. They described extension of peritubular calcium masses into the lumens of tubules in rats given parathyroid extract. "The epithelium overlying calcium might be seen to protrude a little into the lumen. By degrees it advanced, the calcium close behind. The tubules dilated like a celomic cavity. The solid cord of calcium carried the tubular epithelium before it, as fetal gut carries peritoneum; behind it the epithelium formed a mesentery. The mesentery disappeared, leaving a small, solid, calcium-filled, epithelial tube or ball lying free in a larger tube." Anderson [73] described a similar process in a case of hyperparathyroidism with renal calculi in man.

There is general agreement that persons suffering from renal lithiasis deserve to have the possibility of hyperparathyroidism investigated. Barney and Mintz [106] emphasized that in patients with hyperparathyroidism and renal calculi who had been treated successfully by surgical operation stones did not recur.

Comment.—Certain other conditions occasionally produce calcium deposits in the kidney and may result in a renal lesion similar in this respect to that of hyperparathyroidism. Certain skeletal diseases, such as multiple myeloma, have produced renal calcium deposits. Experimental administration of excessive amounts of vitamin D has produced very similar renal lesions, but no well authenticated cases of such lesions following administration of this vitamin in man have been described.

The renal lesions in multiple myelomatosis have been studied by Geschickter and Copeland,[109] Perla and Hutner [110] and Forbus and his associates.[88] Perla and Hutner stressed the presence of nephrosis and calcium deposits in the renal tubules. This localization is apparently dependent on the degenerative changes associated with increased concentration of calcium in the tubular urine. The obstructive features, as stressed by Forbus in his consideration of this lesion, have already been mentioned; in this lesion they seem dependent on protein casts rather than on calcium casts as in hyperparathyroidism.

There is some confusion regarding the changes which may be produced in the kidney by experimental hypervitaminosis D. Much of the early work was done with preparations which contained a large proportion of other sterols (e. g., toxisterol) more toxic than calciferol. As a result, it is uncertain whether many of the lesions described were due to vitamin D or to toxisterol. Considerable doubt may be felt about the cases of death in infancy due to hypervitaminosis D as reported by Putschar [111] and by Thatcher.[112] While the exact dose of vitamin D in these cases cannot be estimated accurately, it does not seem to have been of an order that has been found toxic with the recent pure forms of vitamin D. Calcium deposits such as those described in these cases have been shown by Anderson [73] to be not uncommon in infants, in association with a variety of conditions.

The renal lesions produced by hypervitaminosis D have been described by many authors, among whom may be mentioned: Spies and Glover [113]; Gough, Duguid and Davies [114]; Reed, Dillman, Thacker and Klein,[115] and Duguid.[89b] A degenerative lesion (nephrosis) and calcification both occur, but the two appear to be largely independent. The calcification frequently affected tubular basement membranes and glomerular capsules, as well as tubular epithelium. In late stages the renal lesions of experimental hypervitaminosis D and hyperparathyroidism may bear a striking resemblance. This suggests that either vitamin D exerts its effects on calcium metabolism by way of the parathyroid glands or the disturbance in calcium metabolism in the two conditions is the main factor in the production of the renal lesions. The question

109. Geschickter, C. F., and Copeland, M. M.: Arch. Surg. **16**:807, 1928.
110. Perla, D., and Hutner, L.: Am. J. Path. **6**:285, 1930.
111. Putschar, W.: Ztschr. f. Kinderh. **48**:269, 1929.
112. Thatcher, L.: Edinburgh M. J. **38**:457, 1931.
113. Spies, T. D., and Glover, E. C.: Am. J. Path. **6**:485, 1930.
114. Gough, J.; Duguid, J. B., and Davies, D. R.: Brit. J. Exper. Path. **14**: 137, 1933.
115. Reed, C. I.; Dillman, L. M.; Thacker, E. A., and Klein, R. I.: J. Nutrition **6**:371, 1933.

as to whether or not vitamin D produces its effects by way of the parathyroid glands has been thoroughly discussed recently by Best and Taylor [116] and by Shelling [50] and will not be reviewed here except to say that the weight of evidence appears to be against this hypothesis. If, then, two conditions produce by independent methods similar disturbances in calcium metabolism and also produce similar renal lesions, it suggests that in hyperparathyroidism the disturbance in calcium metabolism may be the essential factor in the production of the kidney disease.

SUMMARY

The parathyroid glands and the kidneys have a close functional relationship. One of the first and most characteristic effects of the administration of parathyroid extract is an increase in renal secretion of phosphate. Deficiency of renal function stimulates hyperplasia and hyperfunction on the part of the parathyroid glands. The actual stimulating factor is not definitely known but is probably some disturbance of calcium or phosphorus balance resulting from the renal deficiency. Parathyroid hyperplasia and hyperfunction are probably present in some degree in all cases in which there is deficiency of renal function. If the disturbance is severe and long continued, a clinical picture characteristic of osteitis fibrosa cystica, in adults, or renal rickets, in children, is produced. These conclusions have received both clinical and experimental confirmation.

Hyperparathyroidism may produce renal lesions of a distinctive type and result in renal failure. Such hyperparathyroidism may be due to a localized adenomatous overgrowth of a single parathyroid or to a peculiar diffuse hypertrophy of all the parathyroids. The resulting disturbance in calcium metabolism appears to be the main cause of the damage in the kidney, though other factors may also have some part in the development of the renal disease. Calcium deposits in the kidney are the characteristic feature. In acute hyperparathyroidism the calcium may be mainly intratubular, but in chronic hyperparathyroidism it is interstitial and peritubular and is accompanied by interstitial fibrosis and cellular infiltration. Damage to the kidney appears to be mainly the result of tubular obstruction. Renal calculus formation is very frequent and develops on the basis of parenchymal calcium concretion. Hyperparathyroidism is, however, the underlying cause of only a very small proportion of renal calculi.

116. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice: A University of Toronto Text in Applied Physiology, Baltimore, William Wood & Company, 1937, p. 1111.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, Etc.—Charles C. Okell, formerly professor of bacteriology at the University College Hospital Medical School, London, died on February 9 at the age of 50.

Georg Strassmann, formerly extraordinary professor of forensic and social medicine in the University of Breslau (Germany), has become a member of the department of forensic medicine in New York University.

The Rockefeller Foundation has made a grant of $2,000 for the continuation in 1939 of the studies on malaria by William H. Taliaferro at the University of Chicago.

According to *Science*, the Commonwealth Fund has made a grant of $8,360 to the Institute of Pathology at Western Reserve University to support for a year studies on the chemistry of immunity under E. E. Ecker. Progress may lead to similar grants for two more years.

Society News.—The annual meeting of the American Society of Clinical Pathologists will be held in St. Louis, May 12, 13 and 14. The seminar will be held on Sunday, May 14. The Hotel Desota will be the headquarters.

The twenty-fourth annual meeting of the American Association of Industrial Physicians and Surgeons with the American Conference on Occupational Diseases and Industrial Hygiene will be held at the Hotel Statler, Cleveland, June 5, 6, 7 and 8, 1939. Information regarding hotel accommodations, etc., may be obtained from A. G. Park, 540 North Michigan Avenue, Chicago.

The third International Congress for Microbiology will be held in the Waldorf-Astoria Hotel, New York, Sept. 2-9, 1939. The general secretary is Dr. Martin H. Dawson, 620 West 168th Street, New York City.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Congenital Universal Insensitiveness to Pain. F. R. Ford and L. Wilkins, Bull. Johns Hopkins Hosp. **62**:448, 1938.

Three cases are reported in which there occurred in children between the ages of 7 and 8 years a congenital indifference to potentially painful stimuli, leading on one occasion to severe burns, multiple fractures and other serious injuries. Except for the disregard of pain, the authors were able to demonstrate no other evidence of disease or defect of the nervous system. They give various reasons for their belief that these children do not have true analgesia but present a defective reaction to the crude sensation of pain which makes that sensation a matter to be disregarded. A small number of cases of a similar nature recorded in medical literature are mentioned. The authors are inclined to believe that such a condition represents a congenitally defective development in the sensory system which involves selectively the pain mechanisms and is comparable to congenital color blindness and similar conditions.

From Authors' Summary.

Regeneration of the Malarial Spleen in the Canary After Infarction and After Burning. W. Bloom and W. H. Taliaferro, J. Infect. Dis. **63**:54, 1938.

Infarcts of varying sizes occur sporadically in the spleens of canaries heavily infected with Plasmodium cathemerium. They are essentially hemorrhagic and are associated with propagating thrombi in the splenic veins, which generally extend from the capsule toward the hilus. They probably result from the malarial infection, as all attempts to associate them with bacteria, viruses or intravenously injected india ink have failed.

Practically all such infarcted areas become completely regenerated, as ascertained by laparotomy and by microscopic examination of the tissues. (Less than 1 per cent show permanent scars.) The first stage in the repair and regeneration is the appearance of macrophages between the healthy and necrosed tissue. The macrophages arise from the reticular cells, macrophages and lymphocytes of the adjacent healthy tissue and from hematogenous agranulocytes (lymphocytes and monocytes). The inflammatory process continues until a young scar is formed containing many spindle cells (fibroblasts) and macrophages. This scar is then infiltrated with lymphocytes, which migrate from the healthy spleen and blood vessels or arise in situ by transformation of spindle cells (fibroblasts) into large lymphocytes and by proliferation of local medium-sized and large lymphocytes. Nests of proliferating lymphocytes associated with the smaller arteries give rise to new nodules, and the fibroblasts of the scar become the reticular cells of both the red and the white pulp. The venous sinuses of the red pulp arise from capillaries of the scar. The process is the same whether the infarct is small or large but is slower in the completely infarcted spleen, owing probably to the fact that in the latter, as all of the splenic tissue is dead, the necessary cells must be mobilized from the blood.

The same type of complete splenic regeneration follows experimental burning of a tip of the spleen except that the speed of regeneration is slower, owing probably to the absence of the capsule, and there is greater exudation of heterophils during the early stage of the inflammation and of eosinophils during the late stage, that of repair.

From Authors' Summary.

EXPERIMENTAL LEAD NEPHRITIS. W. EGER, Virchows Arch. f. path. Anat. **299**: 654, 1937.

One series of rats received 1 per cent neutral lead acetate solution subcutaneously. These injections led after a few days to subcutaneous abscesses. The administration of the lead solution was interrupted until the abscesses healed. The longest duration of life was eight months. A second series received subcutaneous injections of a dilute solution of basic lead acetate; the longest duration of life was four and one-half months. In only two of the animals of the series was the kidney macroscopically reduced in size. Tubular nephritis was produced. In this process the formation of intratubular concretions of lead played a part. Glomerular and vascular changes were not observed.

O. T. SCHULTZ.

EFFECTS OF PARENTERAL INTRODUCTION OF PROTEIN AND NONPROTEIN COLLOIDS. H. HEINLEIN, Virchows Arch. f. path. Anat. **299**:667, 1937.

The protein substances used in these experiments were caseosan (a product that is essentially a 5 per cent solution of casein), horse serum and killed growths of the dysentery bacillus. The nonprotein materials used were trypan blue, thorium dioxide and colloid preparations of copper, bismuth and silicon. Rabbits were used. The material was injected into the ear vein over a prolonged period at intervals that did not lead to shock. Following the injection of the protein substances, parenchymal damage extending to localized necrosis and final fibrosis was observed in the liver and myocardium. More striking was the inflammatory reaction in the arteries of the lung, heart, kidney and liver. This consisted in subendothelial proliferation of histiocytes, lymphocytic infiltration of the adventitia and fibrinoid swelling of the media. This panarteritis, which may simulate closely the histologic picture of periarteritis nodosa, is similar to the hyperergic inflammatory reaction of specifically allergic animals. It is probably due in each case to the action of protein split products. Following injection of the nonprotein colloids, the inflammatory reaction varied in severity with the toxicity of the substance and the degree of vital storage by the reticuloendothelium. Injury to endothelium caused increased capillary permeability and serous inflammation. Other changes were similar to but not so marked as those elicited by the proteins. Protein split products derived from host tissues by the action of the injected nonprotein material are believed to be a factor in this part of the inflammatory reaction.

O. T. SCHULTZ.

Pathologic Anatomy

VITAL STAINING OF CONNECTIVE TISSUES. L. S. KING, J. Exper. Med. **68**:63, 1938.

Trypan blue injected intravenously is bound almost at once by the intercellular connective tissue elements all over the body—by collagen, reticulin and elastic fibers. This union of dye and tissue elements is the factor responsible for the early macroscopic blue color and is antecedent to cellular colloidopexic action. Different specimens of connective tissue differ among themselves in their ability to hold the dye. Diffuse staining of elastic fibers, noted by previous observers, is merely a special example of the general affinity of connective tissue for the dye. The evidence suggests that histiocytes are cells specialized to segregate noxae that become diffusely bound to the intercellular connective tissue matrix.

FROM AUTHOR'S SUMMARY.

EFFECT OF OBLITERATION OF EFFERENT SEMINAL PASSAGES ON THE TESTIS. P. RICHTER, Virchows Arch. f. path. Anat. **300**:225, 1937.

The permeability of the efferent seminal passages was investigated in 525 necropsies on adult males in the course of a year. In 5 of the subjects there

was unilateral obliteration of the vas deferens. In 18 there was occlusion of the epididymis, associated three times with obliteration of the vas on the same side. In 5 subjects the epididymis was occluded on both sides, and in a sixth there was occlusion of one epididymis and of the opposite vas. Thirty-five sterile marriages were recorded for the subjects examined; in only 4 of the men whose marriages were sterile was there bilateral occlusion of the efferent seminal passages as the result of previous gonorrhea such that it could cause sterility. This gives an incidence of 10 per cent, as compared with the usually stated 30 per cent, in which bilateral involvement in the male could be blamed for a sterile marriage. In no instance, whether the obliteration was unilateral or bilateral, was any distubance of spermatogenesis observed unless it was occasioned by the general state or illness of the subject. In unilateral involvement no difference in spermatogenic function was observed in the two testes. In 50 of the 525 subjects spermatozoa were not found in either seminal vesicle, an observation which evidently was the result either of obliteration more distally situated or of chronic inflammation of the vesicles. The presence of spermatozoa in the seminal vesicles of the remaining subjects speaks against the view that the tail of the epididymis is the only place of storage of spermatozoa.

O. T. SCHULTZ.

VENOUS STASIS OF THE MYOCARDIUM. A. THELEN, Virchows Arch. f. path. Anat. **300**:243, 1937.

A discussion of the venous circulation of the heart and of the ways in which it may be impeded precedes a report of a study of 110 hearts selected from a total of 1,000. Myocardial venous stasis is evidenced by a red or brownish red color of the muscle, by escape of droplets of blood from the engorged veins of the cut surface and histologically by engorgement of the veins and capillaries. Stasis is brought about by interference with the pulmonary circulation leading to stasis and increased pressure within the right chambers of the heart. With lesser degrees of involvement of the pulmonary circulation, cyanosis of the myocardium may develop acutely from sudden strain of the right side of the heart. Poor circulation through the coronary arteries leads to stasis, and frequently the condition is seen in the myocardium in elderly persons. Hypertrophy of the left side of the heart is not usually associated with passive hyperemia. Passive congestion leads to fatty change and edema of the myocardium.

O. T. SCHULTZ.

FIBRINOID DEGENERATION OF CONNECTIVE TISSUE. E. BAHRMANN, Virchows Arch. f. path. Anat. **300**:342, 1937.

In a study of fibrinoid degeneration of inflamed tissues Bahrmann found the silver method of the Oliveira helpful. The process is not the result of swelling and homogenization of the connective tissue, with disappearance of the fibrils, as claimed by Neumann, nor to swelling of the collageous ground substance, as claimed by Klinge. The fibers become condensed and compressed. This gives them a density on which the optical properties and the staining reactions of both fibrin and the degenerated tissue depend. Other fibers are swollen as the result of imbibition of fluids containing the soluble precursors of fibrin. Both condensation and swelling may be present at the same time, and transition of one process to the other is evident. Separation of the fibrils of the collagenous tissue by the imbibed fluid causes the fibrils to become argentophilic.

O. T. SCHULTZ.

HEPATOSIS AND ICTERUS. LA MANNA, Virchows Arch. f. path. Anat. **300**:398, 1937.

La Manna includes under the designation "hepatosis" the various parenchymatous degenerative changes that are not part of the inflammatory reaction

The intralobular system of bile canaliculi is considered a differentiated part of the cytoplasm. Nonstainability of the canaliculi is evidence of parenchymatous damage; other evidences are poor staining of the cytoplasm, alterations in the arrangement of the liver cell cords and cytoplasmic inclusions, such as bile or iron pigment granules. Morphologic evidence of parenchymatous damage is not always detectable, even though there are clinical manifestations of dysfunction. Cholangiolosis is a type of hepatosis in which the intralobular system of bile canaliculi is disrupted. Some of the canaliculi may contain bile casts. Cholangiolosis is an important factor in the genesis of icterus. Other factors are dissociation of liver cell columns, dysfunction of the reticuloendothelial system and obstruction.

O. T. SCHULTZ.

MYOEPITHELIAL PROLIFERATION OF MAMMARY DUCTS. R. GUENTHER, Virchows Arch. f. path. Anat. **300**:448, 1937.

The elongated cells with acidophilic cytoplasm lying between the epithelium and the basement membrane of the small and medium-sized ducts of the mammary gland have been termed by Masson, Krompecher and others myoepithelium. Observation of proliferation of this tissue in a breast led to systematic examination of the breasts of 64 women coming to necropsy at the ages of 12 to 79 years and of tissue from 53 women in whom resection had been done because of cystic disease of the breast (mastopathia cystica chronica). In 12 of the necropsy series and in 13 of the surgical series myoepithelial proliferation was observed. The process bore no relation to cystic disease, although the proliferation was somewhat more marked in cystic disease. It was seen in women at or beyond the menopausal age and is held to be one of the several hypertrophic changes that are associated with atrophy of the breast at this period of life.

O. T. SCHULTZ.

ANALYSIS OF SEVENTY CASES OF LYMPHOGRANULOMATOSIS. H. STEPHANI, Virchows Arch. f. path. Anat. **300**:495, 1937.

Stephani presents a statistical analysis of 70 cases of lymphogranulomatosis that were examined post mortem at the Charité, Berlin, Germany, in the years from 1929 to 1936. Of the various lymph node groups, the retroperitoneal was involved in 80 per cent of the cases, as compared with 67 per cent for the cervical group, which is usually held to be the most frequently involved. Of the internal organs, the spleen was most frequently affected in 69 per cent of the cases, the liver next most frequently, in 43 per cent. The lung was involved in 37 per cent—by direct continuity from the mediastinum in 10 and by metastasis in 16 cases. In 3 cases in which there was an association with pulmonary involvement, necrosis had led to cavity formation. The kidney was involved in 17 per cent of the cases—in 8 by metastasis and in 4 by direct continuity. One or both adrenals were affected in 7 cases—only once by metastasis. Gastrointestinal involvement was noted in 23 per cent. Cutaneous lesions were noted in 6 per cent of the cases. In 2 cases the process was held to have been cured by irradiation. The skeleton was affected in 40 per cent of the cases. Bone involvement occurred most often by hematogenous metastasis and infrequently by direct continuity (4 cases). The vertebral column was affected most frequently, in 23 cases, and the femur next most frequently, in 13 cases.

O. T. SCHULTZ.

GENESIS OF CORPORA AMYLACEA OF THE CENTRAL NERVOUS SYSTEM. A. SAXÉN, Virchows Arch. f. path. Anat. **300**:534, 1937.

A controversy exists as to whether the corpora amylacea encountered in the central nervous system are derived from degenerated ganglion cells, axis-cylinders, myelin sheaths or glia. In a previous investigation of the auditory nerve, under-

taken for other purposes, corpora amylacea were frequently seen. In the auditory nerve the bodies are localized to the region of the glial septum between the central and the peripheral portion of the nerve. A systematic study of this portion of the auditory nerve in persons from 50 to 95 years old was undertaken with the aim of determining the origin of the corpora amylacea. In many instances the root of the seventh nerve was also investigated as a control. The bodies appear first as globular swellings of the ends of regenerating axis-cylinders or of split degenerating neurofibrils. The fibrillary glia forms a capsule about each enlargement, which loses its connection with the rest of the axis-cylinder. Proliferated syncytial glia about regenerating axis-cylinders also takes part in the formation of corpora amylacea. Their formation is a phenomenon of senility; local arteriosclerotic changes have an important part in their formation.

O. T. SCHULTZ.

EARLY RENAL CHANGES IN TOXIC NEPHROSIS. C. CORONINI, Virchows Arch. f. path. Anat. **300**:594, 1937.

As an early change in toxic nephrosis Coronini describes swelling of the afferent vessel of the glomerulus and of the stalk of the glomerulus. Mesenchymal proliferation was observed in this region. Although the changes described might be considered a part of an inflammatory reaction, he holds them to be noninflammatory—an evidence of mesenchymal injury in toxic tubular nephrosis.

O. T. SCHULTZ.

RELATION OF CHRONIC INTRACRANIAL PRESSURE TO FATTY CHANGE OF THE LIVER. E. J. KRAUS, Virchows Arch. f. path. Anat. **300**:617, 1937.

In previous publications Kraus had shown that increased intracranial pressure of sufficiently long duration, due to a wide variety of causes, was associated with hypertrophy of the hypophysis if the integrity of the midbrain had not been destroyed by the pressure. Because of the relation of the hypophysis and midbrain to metabolism he made a systematic study of the liver in 36 cases of chronic intracranial pressure. In 80 per cent of the cases the liver revealed the presence of fatty change. Characteristic of the latter was its central location. The cases studied are divided into nine groups, according to the degree of fatty change and its spread from the central zone to the intermediate and peripheral zones of the lobule. The fat was present in the form of large droplets or in that of very fine droplets; most often large and small droplets were intermingled. In 71 per cent of 33 adults the hypophysis was enlarged. The hypertrophy was not associated with any specific type of cell. The chief cells were most often increased in number, and in males this increase was associated with an increase in the number of basophilic cells. The fatty change of the liver bore no relation to the nutritional state of the patient and was not associated with any of the diseases that usually lead to fatty change. The process is held to be due to the influence of the hypophysis and midbrain on metabolism. In many cases the adrenal cortex was hyperplastic and contained an increased amount of lipoid. This is ascribed to increased formation of corticotropic hormone by the anterior lobe of the hypophysis.

O. T. SCHULTZ.

THE STRUCTURE OF THE BASEMENT MEMBRANE. K. MUTO, Virchows Arch. f. path. Anat. **300**:652, 1937.

Muto defines basement membrane as the homogeneous layer which divides connective tissue externally from epithelium and internally from capillaries and muscles. Whether the membrane is fibrillary or homogeneous is controversial. Muto's observations are based on the use of various staining methods, especially the silver impregnation methods. He conceives the basement membrane to be

composed of argentophilic fibrils embedded in a ground substance. The latter may be in the sol state; then it is not visible by any method and may appear as a space in the tissue. Or it may be in the gel state, in which event it is stainable and appears homogeneous or sometimes granular. The size, shape, arrangement and staining properties of the fibrils are not uniform. New formation of the basement membrane was observed in epithelial hyperplasia, both benign and malignant. This may occur by actual new formation of ground substance and fibrils or by rearrangement of the fibrils previously present. Transformation of the membrane may be localized and lacunar. This state may be brought about by liquefaction of the ground substance and rearrangement of the fibrils or by localized disappearance of portions of fibrils and liquefaction of the ground substance. Diffuse transformation of the basement membrane is the result of deposition in the ground substance of amyloid, hyalin or fat.

O. T. SCHULTZ.

Microbiology and Parasitology

FOWL POX VIRUS. G. J. BUDDINGH, J. Exper. Med. **67**:921 and 933, 1938.

Intracerebral inoculation of the virus of fowlpox in young chicks produces within from four to five days a disease characterized by drowsiness and somnolence. These symptoms are followed on the sixth and seventh days by spastic paralysis and convulsions. The majority of inoculated chicks die on the seventh or the eighth day. The pathologic lesions are found chiefly in the meninges, perivascular structures, choroid plexuses, paranasal sinuses, mastoid cells, bone marrow of the cranial bones and orbital tissues. No affinity for nerve tissue per se develops. In this environment the virus has high virulence for the epithelium of the choroid plexus and acquires the capacity of infecting cells of mesodermal origin. All infected cells, of whatever origin, undergo a similar structural change: Fowlpox inclusions appear within them, and they become spherical and detached from one another.

The virus has been carried through fourteen successive intracerebral passages. The symptoms and lesions in chicks inoculated with the virus after the fourteenth passage showed no marked difference from those of the chicks inoculated after the first passage. The changes brought about in the virus by the intracerebral environment do not seem to be enhanced by repeated passages.

Intracerebral transfer of this virus in chicks produces marked changes in the behavior of the virus as studied in the chorioallantoic membrane of chick embryos and in the skin of baby chicks. The virus thus propagated shows a great and persistent increase in virulence for epithelial cells, as evidenced by rapid necrosis instead of proliferation and hyperplasia of these cells. It shows also an affinity for cells of mesodermal origin, including endothelial cells of blood vessels, and an increase in affinity for endodermal cells. The intracerebral virus causes a uniform morphologic change in all types of cells in that the infected cells rapidly become spherical, detached and desquamated, this process being followed by necrosis. One intracerebral passage is sufficient to produce this change in the virus.

FROM AUTHOR'S SUMMARY.

EXPERIMENTAL GONOCOCCIC INFECTION IN MICE AND THEIR PROTECTION BY SULFANILAMIDE. A. COHN and L. R. PEIZER, J. Infect. Dis. **63**:77, 1938.

The mouse may be used in studying chemotherapeutic effects on the gonococcus. There is only one route so far by which the mouse may be infected, namely, the peritoneal. The important factors in experimental gonococcic infection in mice are the preparation of the mucin emulsion, the addition of the dextrose and the choice of the strain of gonococci. The mice used should weigh about 18 to 20 Gm.

The spread of the infection in the mouse follows multiplication of the organisms in the peritoneum, from which the gonococci invade the blood stream. After removal of the peritoneal focus, the organisms disappear from the blood stream.

In current chemotherapeutic studies on gonococcus-infected mice it was found that feeding of sulfanilamide protects mice only when larger doses of this drug are administered than are necessary for subcutaneous injection. When 25 mg. of sulfanilamide was either fed or injected subcutaneously, an average of 65 per cent of the infected mice were protected. FROM AUTHORS' SUMMARY.

PULMONARY SCHISTOSOMIASIS. A. F. B. SHAW and A. A. GHAREEB, J. Path. & Bact. **46**:401, 1938.

In 282 autopsies on Egyptians suffering from schistosomiasis, pulmonary lesions due to ova were found in 33 per cent. The toxic effect of the ovum is shown by necrosis of the tissue in its vicinity. The amount of necrosis varies and possibly depends on the degree of allergy at the time of invasion. The tissues may respond to the presence of ova by reactions other than the formation of tubercles, and it is suggested on the basis of the histologic evidence that the number of ova, reinfection, immunity and allergy may all play a part in determining the type of response. The ova reach the lungs as emboli and become impacted in the arterioles which accompany the respiratory bronchioles, producing a specific actively necrotizing arteriolitis. After necrosis the ovum escapes through the wall of the vessel, and a parenchymatous tubercle forms near the respiratory bronchiole. It is suggested that the ovum secretes an anticoagulant, as it never excites thrombosis.

The number of ova is of primary importance in judging the effect on the pulmonary tissue. In 86 per cent of the cases only a few had entered the lungs, and the only lesions present were parenchymatous tubercles. Embolic ova were rarely seen in these cases. In cases of heavier infection, vascular lesions as well as parenchymatous tubercles were present, and embolic ova were frequent.

Healing of the acute vascular lesions leads to obliterative arteriolitis, often followed by canalization of the occluding tissue. The new-formed capillaries hypertrophy, producing a structure characteristic of pulmonary bilharziasis, to which the authors give the name "angeiomatoid." The vascular changes are focal in distribution. They are unassociated with cardiac hypertrophy or signs of congestive heart failure. Massive and repeated infection of the lungs is followed by widespread arterial changes, hypertrophy of the right ventricle and development of the cardiopulmonary features of Ayerza's disease, with death from congestive heart failure. The severity of the disease is largely due to repeated reinfection of healing or healed lesions. The gross appearances of the lungs are specific only when ova of reinfection fail to complete their migration through the thickened arterioles, with development of tubercles in the walls. At a later stage, when the specific lesions heal, only the effects of long-standing arterial obstruction are evident, and to the naked eye the appearances do not differ from those in Ayerza's disease due to other causes. Microscopically, however, the bilharzial origin can be recognized by the characteristic angiomatoid structure, even although all the ova may have disappeared. The lungs are the seat of chronic passive congestion without hemosiderosis. Two and one-tenth per cent of all cases of schistosomiasis and 6.3 per cent of the pulmonary cases are instances of Ayerza's disease of bilharzial origin. Reasons are given for believing that the latter disease is a common complication in Egypt and other countries where bilharziasis is endemic. Ova of Schistosomum haematobium (58 per cent) are more common in the lungs than ova of Schistosomum mansoni (31 per cent), but S. mansoni produces vascular lesions more often (54 per cent) than S. haematobium (19 per cent). The reasons for this are considered. Evidence is advanced to show that the passage of the ovum through the wall of the vessel is due to necrosis produced by a toxic action of the embryo, the spine playing little or no

part in the process. It has been shown that the ovum can escape through the wall under conditions in which the size of the vessel and the absence of contractility make it impossible for the spine to exercise the piercing function attributed to it by the mechanical theory. Worms were present in the lungs in 3.6 per cent of the series and in 10.5 per cent of the pulmonary cases. Either S. haematobium or S. mansoni may occur. The worms reach the lungs by the pulmonary artery and are usually arrested as riding emboli at the bifurcation of a vessel. Although bathed in venous blood, they die rapidly. While alive, they produce no structural changes, but the dead worm is highly toxic, causing necrosis of the artery and acute focal necrotizing pneumonia. Later the pneumonic exudate is absorbed and cicatrized, but the defunct worm becomes calcified and enveloped in scar tissue.

FROM AUTHOR'S SUMMARY.

Immunology

TUBERCULOSIS IN ALLERGIC AND DESENSITIZED GUINEA PIGS. H. S. WILLIS and C. E. WOODRUFF, Am. J. Path. **14**:337, 1938.

A study of histologic sections from the lungs of desensitized guinea pigs revealed extensive disease with an overwhelming accumulation of acid-fast bacilli. No definite tubercle formation was seen in sections of the liver and spleen. Lesions occurred in the kidneys and blood vessels of both the desensitized and the control animals. It is suggested that the lack of allergy was responsible for the free and unrestrained growth of tubercle bacilli in the lungs of the desensitized guinea pigs.

FROM AUTHORS' SUMMARY.

ACTIVE IMMUNIZATION OF NURSES AGAINST SCARLET FEVER. E. H. PLACE, Am. J. Pub. Health **28**:137, 1938.

Toxin immunization of nurses, when carefully done, largely abolishes evidence of scarlet fever in them during their training in the handling of patients with contagious diseases. There is no evidence that the disease is still occurring in unrecognized form.

FROM AUTHOR'S SUMMARY.

NASALLY INSTILLED POLIOMYELITIS VIRUS. A. B. SABIN and P. K. OLITSKY, J. Exper. Med. **68**:39, 1938.

With a method of intranasal instillation of the virus of poliomyelitis that brings about infection of all rhesus monkeys subjected to it, Sabin and Olitsky undertook a study of the fate of nasally instilled virus in normal and in convalescent, immune animals. Control experiments revealed that the nasal mucosa of normal monkeys contained no observable antiviral factors and that when 5 or 10 minimal cerebral infective doses were added to the mucosa, the virus could be detected by the procedure employed. In the olfactory bulbs even a single infective dose could be recovered, since suspensions of both bulbs could be transferred to the brain of a monkey without any loss of material. After nasal instillation in normal monkeys, the virus disappeared quickly (within four hours or less) and could be recovered neither from the excised nasal mucosa nor from the olfactory bulbs during the first forty-eight hours. At seventy-two hours, just before or coincident with the first rise of temperature, it was found in very small amounts in the nasal mucosa and for the first time also in the olfactory bulbs. At ninety-six hours, at least three days before the appearance of nervous signs, while virus continued to be present in considerable amounts in the olfactory bulbs (and presumably elsewhere in the central nervous system), none was detected in the nasal mucosa. In convalescent, immune animals receiving intranasally the same strain of virus which caused the original infection, none could be recovered from the nasal mucosa or central nervous system at four hours, one, two, three, four, five and seven days. The bearing of these observations on the problem of host to host transmission of the virus of poliomyelitis is discussed.

FROM AUTHORS' SUMMARY.

THE IMMUNOLOGIC BEHAVIOR OF SERUM GLOBULIN. J. MARRACK and D. A. DUFF, Brit. J. Exper. Path. **19**:171, 1938.

The behavior of the water-soluble and insoluble fractions of serum globulin and antiserum to whole serum globulin has been investigated quantitatively. The results suggest that these fractions are not present as such in the whole globulin.

FROM AUTHORS' SUMMARY.

COMBINATION OF VACCINIA WITH ANTIVACCINIAL SERUM. M. H. SALAMAN, Brit. J. Exper. Path. **19**:192, 1938.

Suspensions of vaccinal elementary bodies treated with antivaccinal serum suffer a reduction of infective titer. This reduction persists after all free serum has been removed. The reduction of infectivity is not the result of agglutination of the elementary bodies. The results recorded are consistent with the hypothesis which has been advanced for other serum-virus systems, that under constant conditions a given quantity of antiserum inactivates a constant percentage of any dose of virus on which it acts.

FROM AUTHOR'S SUMMARY.

PRODUCTION OF ANTI-N IMMUNE SERUMS IN RATS. S. OLBRICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**:242, 1937.

Rats inoculated with human red cells NO yielded serums agglutinating human red cells in dilutions varying from 1:40 to 1:320. Absorption with red cells MA gave specific and usable anti-N testing fluids. Attempts to produce anti-M serums failed, and, strangely, from serums of rats inoculated with MO red cells, anti-N testing fluids could be prepared by absorption with M red cells. It cannot be decided whether the readiness to produce agglutinins against the property N and the failure to produce them against M are due to the serologic structure of the rat or to the antigenic properties of the human red cell. The rat shows a similar readiness to produce antibodies against the blood group A and not against B.

I. DAVIDSOHN.

DISTRIBUTION OF BLOOD GROUP FACTORS IN THE TISSUES. V. FRIEDENREICH and G. HARTMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **92**:141, 1938.

Some persons eliminate their blood group factors in certain secretions (gastric juice, saliva, bile, sperm and urine); others do not. The original explanation of this as due to secretion from the blood is invalidated by the finding in glands and tissues of eliminators of large amounts of blood group substances as compared with traces only or complete absence of such substances in the corresponding tissues of noneliminators. In the former group the largest quantities of the group factors (A, B and O) were found in the stomach, submaxillary glands, pancreas and gallbladder; the smallest amount, in the testicles and in the blood. A calculation showed that the quantity of the group factors in the gastric secretion was five hundred times larger than the quantity available in the blood that reached the stomach during the estimated period. The group antigens are produced in the large glands and enter the secretions.

I. DAVIDSOHN.

SEROLOGIC DIFFERENTIATION OF HOMOZYGOTES AND HETEROZYGOTES IN GROUPS A AND B. P. DAHR, Ztschr. f. Immunitätsforsch. u. exper. Therap. **92**:180, 1938.

Homozygotes of group A_1 have the genotypic formula AA, heterozygotes the formula AO, homozygotes of group B the formula BB and heterozygotes the formula BO. Some normal beef serums have specific anti-O agglutinins; when these serums are absorbed with cells A_1B, the anti-O agglutinins decrease only slightly, while a large majority of red cells of subgroups A_1 and B remove a con-

siderably larger quantity of the anti-O agglutinins, and cells of subgroup A_2 remove still more. The proportion of the A_1 and B red cells which remove a great deal of the anti-O agglutinins to those which remove about the same amount as do the A_1B red cells is similar to the incidence of homozygotes and heterozygotes in blood groups A and B which can be expected according to the formulas of Bernstein. The degree of absorption of the anti-O agglutinins in the beef serum corresponds, according to Dahr, to the quantity of the O factor in the genotypic formula. Dahr advocates further absorption studies with red cells of known genotypic formulas: A_1A_1, A_1A_2, A_1A_3 and BB. I. DAVIDSOHN.

Tumors

EFFECT OF 1,2,5,6-DIBENZANTHRACENE ON THE GROWTH OF BROWN-PEARCE RABBIT CARCINOMA. M. APPEL, A. A. STRAUSS, G. KOLISCHER and H. NECHELES, Am. J. Cancer **33**:239, 1938.

In rabbits treated with 1,2,5,6-dibenzanthracene the Brown-Pearce rabbit carcinoma grew more rapidly and metastasized much more extensively than in control animals. The metastases were more numerous, appeared earlier and were found in organs rarely involved in the growth of this tumor, as the spleen, thyroid gland, adrenal glands and myocardium. The proportion of "takes" and the proportion of deaths as a result of carcinomatosis were also increased in the treated animals. The increase in growth of the tumor is attributed to an increase in susceptibility or to a change in predisposition to tumor growth brought about by 1,2,5,6-dibenzanthracene. FROM AUTHORS' SUMMARY.

CARCINOSARCOMA. O. SAPHIR and A. VASS, Am. J. Cancer **33**:331, 1938.

One hundred and fifty-three cases of so-called carcinosarcoma are recorded. A critical review indicates that the carcinosarcomatous nature of these tumors is questionable. Perhaps only 3 or 4 of them may be designated as true carcinosarcoma. A number of observations are given on tumors which were at first thought to be carcinosarcoma but which on more careful examination were interpreted as primary carcinoma. In evaluating the seemingly sarcomatous features of the reported carcinosarcomatous growths, the following four complicating factors which play a role in the alteration of the fundamental histologic appearance of the tumors must be considered: (1) variations of carcinoma cells, some of which assume spindle shapes and may be interpreted as cells of a spindle cell sarcoma, a factor particularly true of "squamous-cell carcinomas with transitional features"; (2) marked anaplasia of carcinoma cells; (3) chronic inflammation which leads to morphologic changes of tumor cells or produces much connective tissue, which may be regarded as part of a malignant connective tissue tumor, or provokes a lymphocytic reaction, sometimes taken as the lymphosarcoma component of the tumor, and (4) invasion of a benign connective tissue tumor by carcinoma. Other instances of so-called carcinosarcoma are believed to be cases of sarcoma invading normal or metaplastic epithelial structures, the latter being interpreted as the "carcinomatous" elements. FROM AUTHORS' SUMMARY.

HIGH INCIDENCE OF SPONTANEOUS MAMMARY TUMORS IN ALBANY STRAIN OF RATS. W. R. BRYAN, G. H. KLINCK JR. and J. M. WOLFE, Am. J. Cancer **33**:370, 1938.

A high incidence of tumors and low fertility have been noted simultaneously in females of the Albany strain of rats during the past eighteen months. The tumors have for the most part been of the benign fibroepithelial type. In addi-

tion, there have been observed: adenocarcinoma, adenoma and fibroma. Three of the fibroepithelial tumors displayed the characteristic picture of intracanalicular adenofibroma.

FROM AUTHORS' SUMMARY.

USEFUL METHODS FOR ROUTINE EXAMINATION OF BRAIN TUMORS. N. C. FOOT, Am. J. Path. **14**:245, 1938.

Foot states that thus far diagnoses have been made of astrocytoma, polar spongioblastoma, glioblastoma of the multiform type, oligodendroglioma, and glioblastoma arising from the adrenal region, with origin in the sympathetic nerves. The last-named tumor would have passed as an unusual form of carcinoma; in fact, it did until silver impregnations demonstrated the structure of the multipolar atrocytes contained in it. Their processes were practically unnoticeable in the sections prepared with the hematoxylin-eosin stain but were better shown in the trichrome sections, which led Foot to try silver impregnation. With this they came out excellently. There is no reason, he says, why the combination of the methods set forth in this paper should not be equally good for ependymoma and those tumors having cells of a more immature type—so-called medulloblastoma and neuroepithelioma. He has found them excellent in the case of meningioma. Naturally, they are also applicable to tumors of peripheral nerves, with which they give splendid results, affording a means of accurate diagnosis.

FROM AUTHOR'S SUMMARY.

COMEDO CARCINOMA OF THE BREAST. D. LEWIS and C. F. GESCHICKTER, Arch. Surg. **36**:225, 1938.

Comedo carcinoma occurs in two rather characteristic forms: diffuse and localized. The diffuse form presents some of the clinical features peculiar to intracanalicular myxoma. It grows slowly and involves the greater part of the breast; no isolated tumor can be palpated in the enlargement. Despite the size of the growth, there are frequently no palpable lymph nodes. Small elevations in the skin may be found, which are caused by the protrusion of the epithelial plugs within the ducts. Not infrequently a discharge from the nipple is noted.

The localized form of the tumor is small, from 1 to 3 cm. in diameter. It is usually situated at the margin of the areola just beneath the skin and is freely movable. The axillary nodes as a rule are not involved. Not infrequently there is a yellowish or watery discharge from the nipple. The affected breast is slightly larger than the uninvolved breast. The tumor differs from intracystic papilloma and blue dome cyst in that it is relatively harder and more irregular.

The age incidence of comedo carcinoma corresponds to the age incidence of other forms of carcinoma of the breast. The location of the comedo carcinoma suggests origin in the larger ducts. Retraction or fixation of the nipple occurs often, and occasionally the patient complains of burning and itching of the nipple, a symptom more common in Paget's disease. The tumor is usually located near the skin, and atrophy of the overlying fat and dimpling of the skin occur. The tumor remains movable. Even when the growth is larger than a large grapefruit and involves almost the entire breast, there will be no fixation to the wall of the chest. Several tumors may be found in the same breast. Of all the forms of carcinoma of the breast, comedo carcinoma offers the most favorable prognosis. Five year cures were obtained in 85 per cent of the patients. The majority of the patients living more than five years after complete operation have remained well for ten years or more.

TRANSMISSION OF THE ROUS FILTERABLE AGENT TO CHEMICALLY INDUCED TUMORS. E. MELLANBY, J. Path. & Bact. **46**:447, 1938.

When a fowl carries a tumor of the type induced by chemical agents, such as dibenzanthracene or tar, and at the same time another tumor of the Rous

type, i. e., of the type produced by a filtrable agent, the Rous factor passes into the chemically induced tumor but leaves it apparently unaffected. If the cells of such a chemically induced tumor are injected into a fowl, they produce a tumor of a structural type which can be propagated further only by inoculation of cells. If a cell-free filtrate of such a chemically induced tumor in a fowl bearing also a Rous sarcoma is injected into other fowls, it produces, if it produces a tumor at all, a tumor of the Rous type. In two of many experiments cell-free filtrates made from the second generation of chemically induced tumors—i. e., tumors which themselves had no association with a Rous sarcoma in the same fowl—produced Rous sarcoma (third generation) which could be propagated further by a cell-free filtrate. Cells of these chemically induced tumors, however, produced other (third generation) tumors of the same type as those originally chemically induced and these gave no evidence of containing the Rous agent. In two experiments second generation dibenzanthracene tumors of fowls regressed and new tumors grew in their place. These new tumors had the character of the Rous sarcoma and could be readily propagated by cell-free filtrates. There is no good reason to believe that the presence of the Rous agent actually made the dibenzanthracene tumors regress, as such regression may occur without the presence of Rous sarcoma in the same bird. Injecting the Rous filtrable agent into a dibenzanthracene tumor will not make it regress but may produce Rous sarcomatous tissue in it. It appears, however, that when regression takes place, the Rous agent exerts its effect and produces a second Rous tumor replacing the dibenzanthracene tumor.

FROM AUTHOR'S SUMMARY.

PREVENTION OF MAMMARY CANCER IN MICE BY THYROTROPIC PITUITARY HORMONE. W. CRAMER and E. L. HORNING, Lancet **1**:72, 1938.

The thyrotropic principle of the pituitary has been used to prevent the development of mammary cancer in cancer-susceptible mice. The thyrotropic principle has also been used to prevent the changes in the pituitary and mammary glands of male mice caused by estrogen. These observations may prove of value in the treatment of cystic disease of the breast supposedly caused by estrogen.

CANCER IN MADAGASCAR. G. MOUSTARDIER, Bull. Assoc. franç. p. l'étude du cancer **27**:24, 1938.

Cancer is not as infrequent among the natives of Madagascar as was claimed by some previous writers. The author studied 87 tumors in eighteen months, all of them among the natives. Twenty-five were benign; 14 of these were epithelial, 9 of connective tissue origin and 2 mixed. Sixty-one were malignant: 45 of these were carcinoma, 11 sarcoma, 2 melanoma, 1 glioma, and 2 were embryonal tumors. The absence of tumors of the lips, tongue, mouth and pharynx was the more striking in view of the fact that such tumors are frequent in Europeans and are easily detected. Syphilis and smoking and chewing, which are commonly held responsible for some of these growths, are very prevalent on the island. The proportion of cases of sarcoma to cases of carcinoma (1:4) was higher than among the white races. The natives rarely reach the advanced age in which cancer is prevalent. Women were afflicted more often (37) than men (24); this is due to the great frequency of cancer of the breast and of cancer of the uterus.

I. DAVIDSOHN.

A MELANOTIC TUMOR IN A FISH. R. P. DOLLFUS, J. TIMON-DAVID and M. MOSINGER, Bull. Assoc. franç. p. l'étude du cancer **27**:37, 1938.

Melanotic tumors occur quite frequently in fish; in a series of L. Thomas, they were present in 15 (57 per cent) of 270 tumors. The one reported now differed in certain essentials from all previously reported examples of melanoma. In a fish belonging to the species Epinephelus gigas many tumor nodes were seen, the

largest the size of a walnut. Most of them were on the gills, but no part of the body was free from them, including the liver, spleen and peritoneum. Histologic preparations showed epithelial masses, mainly in the form of distinct round nodules, some with a peripheral zone of compressed cells. Degenerative changes were abundant and varied. Massive accumulations of a brown granular pigment were seen. They seemed to be of a degenerative nature, but in the hepatic and splenic metastases the melanotic deposits were similar to those seen in true melanotic tumors. The authors believe that this is essentially an epithelial tumor the cells of which have acquired melanogenic properties secondarily.

I. DAVIDSOHN.

TISSUE CULTURE OF LYMPHOGRANULOMA (HODGKIN'S DISEASE). R. MEIER, E. POSERN and G. WEITZMANN, Virchows Arch. f. path. Anat. **299**:329, 1937.

In cultures lymphogranulomatous tissue grows more rapidly and more actively than normal lymphoid tissue in vitro. Fibrocytes grow out from the explant and produce a fibrillated zone similar to that of normal lymphoid tissue. In this zone are small lymphocytes and larger round cells with granular cytoplasm. The latter are held to be pathologic large lymphocytes. There also appear in the culture many large giant cells, which are often multinucleated. They are at first homogeneous and optically indistinct but undergo a sudden transformation which makes them less homogeneous and more readily visible. These cells are like the Sternberg-Reed giant cells of lymphogranulomatous tissue, but the authors do not definitely establish the observation that the tissue culture giant cells and Sternberg-Reed cells are identical. When normal lymphoid tissue and lymphogranulomatous tissue were grown side by side in the same culture flask no formation of giant cells by or from the normal tissue was observed. The formation of the giant cells in tissue culture is a fixed and irreversible property of the cells and is characteristic of lymphogranulomatous tissue. It is a property similar to or identical with that of tumor cells. The authors think that the giant cells of the tissue culture are derived from endothelial cells.

O. T. SCHULTZ.

BENIGN BRONCHIAL TUMORS. H. HAMPERL, Virchows Arch. f. path. Anat. **300**: 46, 1937.

In 1931 Geipel described as benign basal cell epithelioma 2 bronchial tumors and collected reports of 6 similar benign tumors from the literature. Hamperl describes minutely the gross and microscopic appearances and the clinical manifestations of 9 benign bronchial tumors. These with Geipel's 8 and others described in the literature bring the total to 32. Most of them occurred in persons under 50 years of age. There has usually been a long history of respiratory difficulty, indicating that the tumors usually arise at an early age. The usual clinical findings are those of localized bronchiectasis. The tumor may grow into the lumen as a polypoid growth or may grow within the wall of the bronchus, bulging either outward or inward. In 2 of Hamperl's tumors the histologic picture was identical with that of mucus-secreting cylindroma, such as occurs especially in the salivary glands. The author derives these tumors from mucus-secreting cells of the bronchial mucosa. Each of the other neoplasms had an invasive type of growth within the bronchial wall. They were, however, only locally invasive, did not invade surrounding tissues and did not metastasize. They were composed of solid cords and masses of cells of epithelial type, some tall, of the palisade type, others polyhedral. They also contained cells of the oncocyte type, which Hamperl has previously described in a variety of aging parenchymatous cells. Some of the cells secrete mucus, and some are arranged about narrow glandular lumens. Hamperl considers the structure and morphologic features of these tumors identical with those of the gastrointestinal carcinoid as described by Masson. He therefore terms them bronchial carcinoids. Hamperl admits the theoretic possibility of the develop-

ment of malignancy in the two types of bronchial tumor described, but thus far satisfactory proof of their malignancy has not been adduced. The importance of clinical diagnosis, by roentgenographic, bronchoscopic and histologic examinations, is stressed.

O. T. SCHULTZ.

FORMATION OF RUSSELL BODIES IN PLASMACYTIC MULTIPLE MYELOMA. K. APITZ, Virchows Arch. f. path. Anat. **300**:113, 1937.

Different kinds of cellular degeneration products occurring in a variety of cells have been called Russell's bodies. Apitz insists that the typical fuchsinophile body is formed only in the plasma cell. The latter must have the morphologic appearance described by Unna and must give the charactseristic pyronine–methyl green staining reaction. In a cytologic study of material in 14 cases of multiple myeloma, the formation of Russell's bodies was observed in 4. In 2 instances the cells were typical plasma cells, whereas in 2 the cells were immature. The presence of fuchsinophile bodies in the latter establishes the plasmacytic character of these tumors and is considered proof that plasma cells may differentiate from myeloblasts. The formation of Russell's bodies within the nucleus is described by Apitz. Neither chromatin nor nucleolar substance takes part in their formation. Russell's bodies are held to be the result of abnormal intracellular metabolism of protein.

O. T. SCHULTZ.

SIMILARITY OF CORTICAL GLIOMA AND PIAL MENINGIOMA. H.-H. MEYER, Virchows Arch. f. path. Anat. **300**:296, 1937.

Four cases are described in which it was impossible to determine from the gross characteristics whether a tumor was a glioma that originated in the cortex of the brain and invaded the meninges or a meningioma that originated in the pia-arachnoid and invaded the brain. For meningioma the author prefers the term "arachnothelioma." Microscopic examination after the use of special staining methods established that the tumors described were gliomas. One was astrocytoma and one astroblastoma. Two were glioma multiforme. The gross similarities and microscopic differences of cortical glioma, meningioma and meningeal glioma are discussed.

O. T. SCHULTZ.

Medicolegal Pathology

THE MEDICOLEGAL EXAMINATION OF HAIRS. B. M. VANCE, New England J. Med. **218**:914, 1938.

In general, the evidence which results from examinations of hair must be regarded as confirmatory. It should never be used unsupported by other proof. The circumstances in each case must determine how valid will be the facts elicited by examination of the hair. The most fitting person to perform examinations of hair is a graduate of a medical school or a biologist of wide experience. The study of hair is a branch of histology of such complexity that long and painstaking application is required to master it. It is important that the scientist engaged in this pursuit should prepare numerous specimens of human and animal hairs, both in whole mount and in cross section and that he should make photomicrographs of the most typical specimens for the purpose of ready comparison.

FROM AUTHOR'S SUMMARY.

PATHOLOGIC-ANATOMIC STUDIES OF SO-CALLED DURET-BERNER HEMORRHAGES. B. DAHL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:366, 1938.

The investigations reported indicate that a deadly blow on the head results in immediate general distention of the veins and venules, the circulatory disturbances leading to edema in the inner organs. In the lungs and mesentery hemorrhages

occur. Simultaneously with the circulatory disturbances or even shortly before their onset, respiration ceases and cardiac function becomes superficial, rapid and irregular, and eventually stops. Such alterations occurring in death agony from other causes set in slowly, but in severe injuries of the head they occur almost instantaneously. The tonus of the blood vessels, especially that of the abdominal veins, disappears rapidly, and blood accumulates in these veins as the arteries and capillaries contract and empty themselves. Similarly, blood collects in veins of the brain, subjecting them to the possibility of rupture, especially on the cerebral surface and in the spongy subependymal tissue. These hemorrhages, therefore, are not the cause but the result of death.

There is no destruction of ganglion cells following the rupture of agonally distended veins. Agonal hemorrhages are found regularly in the brain, in the pia and under the ependyma of the ventricles, also in the fourth ventricle. In hemorrhages of the fourth ventricle (Berner hemorrhages) it is impossible to say whether death resulted from trauma of the head or not.

GEORGE J. RUKSTINAT.

CUTANEOUS MARKINGS FROM PLUNGES INTO WATER. A. PONSOLD, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:408, 1938.

Definitely outlined longitudinal light streaks, bordered by raised red ridges, have been noted on the legs of persons striking water after jumping from high bridges. Sometimes the ridges are studded with hemorrhages. Similar but round spots may be found on the buttocks. In persons who survive such accidents, the condition increases in intensity for twenty-four hours, then gradually subsides. In about four days the skin changes vanish. Balázs expressed the belief that the alterations in the skin result from pressure by articles of clothing. Other observers were convinced that the longitudinal stripes are a projection of the long bones on the surface of the skin. There is anemia at the site of impact because the bones exert a pressure against the skin toward the outside. Because of local anemia in the zone of compression, the adjacent vessels are overdistended and produce the red ridges. The red spots on the buttocks are projections of the foramina obturata. The shift of blood is a vital or agonal reaction and remains when death occurs quickly. The skin changes offer a method of determining the site of impact. Ponsold found the same dermal patterns on the body of a woman who fell from a third floor window to a brick sidewalk.

GEORGE J. RUKSTINAT.

THE IDENTIFICATION OF PERSONS BY THEIR BITES. BUHTZ and EHRHARDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:453, 1938.

Teeth, because of their hardness, usually are well preserved. Their characteristic arrangement, therefore, may provide identifying marks. The physiologic evolution of teeth furnishes the best gage of age up to 16 years. Later in life, the wear of teeth surfaces, the increased calcification of the root canal and the recession of the alveolar processes are roughly indicative of age. The smaller size of women's teeth furnishes a suggestive but not infallible guide to age. Caries and discolorations of a characteristic type appear in candy makers, chemical workers and metal workers.

The identification of a person from his bite is facilitated when gross anomalies are present in the position, form or number of his teeth. The records of dentists frequently are helpful, since they definitely localize fillings, crowns, bridges or extractions. Burglars have been identified by the impressions their dentures left on food in the place they burglarized.

The methods employed to identify a person who has bitten another have heretofore not proved dependable. The authors believe they have a method which overcomes many of the difficulties. First, they take photographs of the bites in the victim's skin by side illumination and accurately measure distances from the lens,

etc. Second, they make use of a phantom arm made of wood and covered with rubber. This is coated with an egg and flour batter, and the bites of suspected dentures on this arm are compared with the photograph of the wound of the victim. Third, diapositive films are made of the suspected teeth. The films may be superimposed on the original picture or laid on white paper, for comparison.

GEORGE J. RUKSTINAT.

THE MEDICOLEGAL SIGNIFICANCE OF THE CUTANEOUS ELASTIC FIBER SYSTEM. S. ÖKRÖS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:485, 1938.

Ökrös fixes skin in a stretched state so that the elastic fibers will be straightened and occur at regular intervals. The elastic fiber system of the skin has a static portion connected with the collagenic fibers and a parenchymatous part enmeshing the sweat glands, nerves and blood vessels. Because of the stocking-like investment of the papillae of the skin the subpapillary elastic fibers do not straighten and therefore do not lend themselves to study.

In wounds produced during life, shortly after death and at periods up to ten days after death the changes that occur in the deeper layers of the cutis are constant. In stab wounds produced during life the meshes of the elastic net are torn, especially in the corners of the wound. The individual fibers are split, wound spirally and in places tied in knots. In the outer part of the wound oral swellings occur on the meshwork. These changes are proof that elastic fibers torn or cut during life retract, roll together and twist. Experimental wounds produced on the same body ten hours post mortem showed the elastic fibers retracted from their wound margins, but swelling, spiraling and twisting were absent. A wound made ten days after death showed only a little retraction of the fibers.

In bullet wounds there are discontinuity of the fibers and shattering of tissue, due to explosive action. At the moment of entrance into the skin a bullet transmits its enormous kinetic energy through the tissues so that there is a rupturing of the meshes not only in the wound but at a considerable distance from it.

GEORGE J. RUKSTINAT.

TRAUMATIC PNEUMOPERICARDIUM. O. BERNER, Virchows Arch. f. path. Anat. **299**:751, 1937.

A 4 year old lad who had been struck by an automobile died within ten minutes after reaching a hospital. A moderate degree of subcutaneous emphysema was noted, but this had disappeared at the time of necropsy by the medical examiner, twenty hours after death. There was no emphysema of the mediastinum. The right pleural cavity contained blood and air, and the lung was ruptured posteriorly. The pericardial cavity contained air. There were no adhesions between the pleura and the lung at the site of rupture of the lung. The explanation offered is that the injury caused pneumothorax and compression of the chest, which forced air through the parietal pleura, leading to subcutaneous emphysema, and through the posterior part of the pericardium, where a rent 2 cm. long was found. There were no rib fractures that might have caused emphysema.

O. T. SCHULTZ.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

ALFRED PLAUT, *President*

Regular Monthly Meeting, Dec. 22, 1938

ROBERT A. MOORE, *Secretary*

CAVERNOUS TRANSFORMATION OF THE PORTAL AND SPLENIC VEINS. AMOUR F. LIBER and CHESTER R. BROWN.

An apparently healthy white man, 20 years old, suddenly began to have hematemesis, which repeatedly seemed to threaten his life. One year before death he had pneumococcic lobar pneumonia. The spleen became palpable. Anemia and thrombopenia were reported. Osteomyelitis of the tibia appeared. No other focus of infection could be discovered. Following splenectomy there was no hematemesis for five months, but ascites developed (3,500 cc. of abdominal fluid). Omentopexy was performed. During this operation there was a "matted feeling" about the portal vein. The ascites disappeared promptly, but the patient succumbed to renewed hematemesis fourteen months after the onset of the symptoms.

The spleen weighed 530 Gm. Sections near the hilus showed localized thickenings of the intima of the large veins. Liver tissue removed at the first operation was normal. A specimen of liver taken for biopsy at the second operation revealed lymphocytic infiltration and mild patchy fibrosis of the portal spaces.

Necropsy revealed large varices in the diaphragmatic portion of the esophagus. About the entire stump of the splenic vein and the initial 2 cm. of the portal vein was a large, fairly firm, very elastic mass of brownish pink tissue containing innumerable vascular spaces of all sizes, from a diameter of 5 mm. down to the limits of gross visibility. From several of these cavities small phleboliths could be shelled out. This spongy mass measured about 5 cm. vertically and 15 cm. transversely. It extended upward beneath the parietal peritoneum of the lesser sac to the level of the terminal portion of the esophagus, which it partially surrounded. The interior of the portal vein presented several small folds in the intima, which formed a loose network in the proximal centimeter of the vein, where the lumen was moderately narrowed. The splenic vein showed the same type of trabeculation. The intimal folds became more and more numerous and extensive toward the proximal end of the splenic vein. In many places the lumen was subdivided into four or five channels. Microscopically the spongy perivenous tissue revealed innumerable veins of varied sizes and irregular outline. Many contained thrombi in all stages of organization. Between the channels were thick septums of connective tissue, very rich in elastic fibers, fat, nerves and small blood vessels of normal appearance. The intravenous trabeculae were made up of long bands of collagen and fibroblasts, between which were fine elastic fibers and numerous foamy lipophages containing isotropic material staining with scarlet red. At the point of implantation of a trabecula the internal elastica of the vein bulged out but was not interrupted. The underlying muscle layers were dissected by fibrosis. The liver showed very slight, patchy lymphocytic infiltration and fibrosis of the portal spaces. Near the base of the posterior aspect of the left lung was a subpleural mass measuring 3 cm. in diameter and having exactly the gross and microscopic appearance of the periportal tissue. This case poses once more the much discussed question whether cavernous transformation of the portal vein is a congenital anomaly or a canalized thrombus and collateral circulation. The presence of cavernous tissue in the lung suggests multiple vascular malformation. The lack of a favorable effect of splenectomy is of interest, since thrombocytemia, which Klemperer (ARCH. PATH. **6**:353, 1928) stated is a contraindication to splenectomy, was not present in this case.

A second case was one of portal thrombophlebitis with multiple abscesses of the liver and portal cirrhosis. There was chronic pulmonary tuberculosis. The portal vein was divided into two unequal channels by a longitudinal septum. To the distal margin of the septum was attached a thrombus, well organized at its base but fresh and suppurating distally. The microscopic structure of the septum was similar to that of the trabeculae in the first case. An additional feature was patchy calcification. Here the relations suggest strongly that the single septum was a preexisting anomaly on which the thrombus was grafted. A similar septum without any thrombus was observed in the femoral vein by Gibson and Franklin (*J. Anat.* **72:** 128, 1937). Klemperer reported 23 cases of portal cavernoma, including a case of his own. The first case in his series was that of Köbrich. An older case has been found, reported by Verneuil (*Bull. Soc. anat. de Paris* **28:**246, 1853). Since Klemperer's report, 8 cases have been published in addition to those reported here.

Dr. Maurice Richter supplied some of the material for the first case report.

BRONCHIOLAR NECROSIS IN THE NEWBORN. SHELDON A. JACOBSON.

A full term boy was born spontaneously at 2:40 a. m. He was given routine care and cried lustily. At 6 a. m. his general condition was good. Later in the morning, however, cyanosis supervened, with labored respiration and retraction of the episternal notch. The diagnosis of atelectasis of the left side was made.

Despite the use of an oxygen tent and injections of alpha lobeline and epinephrine hydrochloride, the infant became progressively feebler, and he died twelve hours after birth.

Autopsy disclosed atelectasis of both lungs. Pieces cut from different parts of the lungs sank in water. Microscopic section showed most of the pulmonary tissue collapsed. In the alveoli were many squamous epithelial cells and other débris. The respiratory and terminal bronchioles showed widespread necrosis of their walls, but there was no necrosis of the adjacent areas of the lungs. There was no indication of an exudative or other reaction.

The localization of the lesions and the absence of cellular infiltration speak against vascular occlusion or infection as etiologic factors. It is postulated that in the course of prenatal respiration (the occurrence of which is established by the intra-alveolar débris) the infant aspirated some of its own activated gastric or intestinal juice, which led to lysis.

DISCUSSION

PAUL KLEMPERER: Was there fat in these bands? Did you stain for fat?

SHELDON A. JACOBSON: Fat staining was not done. There were no clear spaces.

PAUL KLEMPERER: I ask because I am not quite clear as to whether the changes observed by Dr. Jacobson are identical with the hyaline bands which were described in the lungs of the newborn in a recent article. The author described hyaline bands in the newborn in 4 cases, and the bands in the illustration not only resemble very much the hyaline bands which are found in cases of rheumatic fever but also in cases of chronic passive congestion of severe degree. His explanation was that aspiration of amniotic fluid is responsible. However, what Dr. Jacobson assumes is, I think, possible. I remember an infant who died a few weeks after birth, following severe hematemesis, and there were similar lesions, but these were actually necrotic lesions and one could see aspirated gastric contents in this case.

IRVING GRAEF: I should like to confirm what Dr. Klemperer has just said and, in addition, mention the excellent work of Farber on hyaline membranes in the lungs of newborn infants. Before Farber, Johnson and Meyer described these findings in the lungs, together with typical epidermal cells, vernix caseosa and meconium, as commonplace in newborn and stillborn infants. The membrane

shown here resembles the hyaline membrane mentioned. I am not certain whether or not necrosis takes place beneath these membranes, but I have seen it quite frequently without any inflammatory response. It is possible that, since the vernix is lipid, some lipolysis may take place and lead to chemical inflammation. Since the newborn infant's gastric juice is virtually free from hydrochloric acid or lipase, it is unlikely that gastric contents play much of a role in pulmonary inflammation, when it is present. It seems to me that in cases of congenital pneumonitis more attention should be paid to the condition of the amniotic fluid and membranes. Often the physician studies the infant carefully and fails to go back to the study of the amniotic membranes as the possible source of infection or of leukocytes.

ALFRED PLAUT: I agree with Dr. Klemperer and Dr. Graef that in all probability what Dr. Jacobson has shown is the same thing as the so-called hyaline layers. My colleagues and I see them quite frequently in our material from newborn infants, and, if I remember correctly, there is no direct connection with any pathologic condition in the mother. We also have seen them in the lungs of several adults, but never in the lungs of patients with rheumatic fever. It probably is just a coincidence that the membranes in the lungs of persons dying of hydrochloric acid poisoning are so very similar to these. Probably the two lesions are morphologically identical but of different genesis.

PAUL KLEMPERER: I am very glad that Dr. Plaut says he did not find these hyaline layers in the lungs in rheumatic fever. I have been trying to find them, and it may be recalled that a year ago there appeared an article by Masson in which he claimed these hyaline membranes were characteristic of rheumatic fever. I never believed it, but I must confess I have seen them in the lungs in rheumatic fever. However, I do not think they are characteristic of rheumatic fever but are characteristic of a peculiar stage of chronic edema and inflammation in the lung in rheumatic fever. It interests me that Dr. Plaut has not seen these hyaline membranes in the lungs in rheumatic fever.

OSSEOUS FINDINGS IN CHRONIC RENAL INSUFFICIENCY IN ADULTS. ARTHUR M. GINZLER (by invitation) and HENRY L. JAFFE.

It is known that the parathyroid glands become enlarged secondarily in so-called renal rickets of children and in chronic renal insufficiency of adults. Our postmortem observations confirm this knowledge. Furthermore, there is experimental evidence to support the hypothesis that the parathyroid hyperplasia is caused by the hyperphosphatemia that is a feature of these conditions.

The pronounced osseous changes occurring in cases of renal rickets are well known and have been adequately described. Extensive osseous changes, have also been observed in a few cases of chronic renal insufficiency, in which they have usually been denoted as "generalized osteitis fibrosa." In these cases, there was pronounced enlargement of the parathyroids, such as one sees also in cases of renal rickets. Altogether, the osseous findings in these cases in adults may be regarded as the adult equivalent of those noted in cases of renal rickets of childhood. In the presence of such pronounced osseous changes, secondary hyperparathyroidism can safely be inculpated as a contributory causal factor.

The cases with which we are concerned here, however, are those of chronic renal insufficiency in which there are bone changes not clearly ascribable to parathyroid hyperfunctioning, even though associated with some degree of parathyroid enlargement or at least microscopic hyperplasia. Our observations in regard to these cases may be summarized as follows: The bones, though usually not altered grossly, often reveal on microscopic examination mild but clearcut fibroporotic changes in the spongiosa. In these cases, the spongy trabeculae show scattered resorption lacunae containing osteoclasts and connective tissue, and some of them may also present, here and there, deposits of new bone. Occasionally—and specifically when the renal insufficiency has been very protracted—the bones will be found even grossly altered. In these cases, the spongiosa is close meshed, and the trabeculae are thickened and distorted, so that altogether the condition

amounts to osteosclerosis. The microscopic observations indicate that the osteosclerosis has developed through gradual accretion of new bone, despite the alternation of reparative with resorptive processes that must have been going on for a long time.

Only Rutishauser and his associates have described osseous changes sometimes rising to the level of osteosclerosis in patients in whom secondary hyperparathyroidism was probably not an important factor in the development of the bone lesions. There is no experimental proof that the parathyroid hyperplasia in these cases is accompanied by hyperfunction. This fact, together with the mildness of the hyperplasia in our patients, convinces us that the osseous changes described are probably not caused by the action of increased circulating parathyroid hormone on the bones. This conviction is strengthened by a comparison of these osseous changes with those in Recklinghausen's disease. As noted, an increase in circulating parathyroid hormone does seem to be a complicating factor in patients with pronounced enlargement of the parathyroids. In regard to the cases under discussion here, however, we feel that the osseous changes resulted from the chronic acidosis due to the renal damage, and specifically that demineralization of the skeleton followed the forced excretion of fixed base which is necessary to eliminate the acid end products of metabolism.

DISCUSSION

PAUL KLEMPERER: These bone changes in chronic renal insufficiency have been noted by me for years. My associates and I have found the condition most striking in patients with malignant nephrosclerosis. I do not remember whether these patients had a longer period of renal insufficiency than usual. It is interesting that malignant nephrosclerosis, which is not an instance of long-standing renal insufficiency, should give rise to the same changes as illustrated here in chronic renal insufficiency.

H. L. JAFFE: I think it is worth emphasizing that the osseous changes described (including the osteosclerosis) are not detectable roentgenologically in the living subject. Even when autopsy showed advanced osteosclerosis, the sagittally sectioned vertebral column when roentgenographed did not show any clearcut modification of the normal roentgen picture.

ARTHUR M. GINZLER: We saw these changes in 1 of 3 cases of malignant nephrosclerosis examined, but it was our impression that the changes were most commonly observed in cases of chronic pyelonephritis secondary to prostatic obstruction, in which, perhaps the conditions for the development of long-standing renal insufficiency were most favorable.

HISTOGENESIS OF MAMMARY CARCINOMA: A STUDY BASED ON KEY BLOCK SECTIONS OF THE WHOLE GLAND. HAROLD KOPPELMAN (by invitation).

An adaptation of Fraser's key block method (*Surg., Gynec. & Obst.* **45**:266, 1927) was used in a study of 8 cases of cancer of the breast, under the direction of Dr. Irving Graef. Each complete breast dissected was cut into serial sections 0.5 to 1 cm. in thickness, and after fixation an average of 34 key blocks were cut for microscopic study, their locations being marked on a drawing or photograph of the gross specimen for orientation of the features observed. For each specimen a schematic serial reconstruction was drawn, illustrating the gross anatomy of the tumor as checked by microscopic observation. This method provided a broad yet quite detailed view of each gland and yielded a series of observations which usually escape notice in the ordinary random review of breast material.

The origin was in each case traceable to duct epithelium at some point confined within normal boundaries, usually an expanded cystic papillary lesion. Secondary spread occurred both within the ducts and through their walls. Multiple foci of origin were observed in 1 case and suggested in 3 others. Intraductal spread extended in 1 case for a distance of 5 cm. and was observed in 3 others at some distance from the primary growth. This mode of spread also accounted for the involvement of lobular (acinar) epithelium which occurred in 6 cases.

Invasive spread from the ducts outward was easily demonstrable, but invasion from cancerous acini was doubtful. The morphologic aspects of the invasive cells

gave no clue as to their origin from ducts or acini. Local invasion was often seen to be propagated by permeation through lymphatics, often periductal and perilobular in location, accounting for the common finding in random sections of nodules of invasive growth adjacent to normal ducts and for the equally common occurrence of invasion of preexisting lobules sparing the epithelium of terminal ducts and acini. So-called histologic types of breast cancer, such as medullary, scirrhous and adenoid, appeared to be merely different types of invasive spread, coexistent in most of the cases, and probably dependent for their appearance on factors of pressure from the soil the cells invade. These histologic features, as well as the factor of anaplasia, which was seen to vary considerably in different areas, appeared to have no consistent correlation with prognosis.

Clinically unsuspected multiple benign neoplasia was observed in 7 of the 8 cases, including papillary growths, cyst formations, adenoma and fibroadenoma, but only the papillary growths (excluding papillary cysts of the so-called sweat gland type) seemed to be related to the origin of carcinoma. While the lesions of chronic cystic hyperplasia were present in 6 cases, in only 1 was malignant extension traceable to the papillary neoplasia, and in that case multiple foci seemed probable.

The observations in this small series are consistent with the concept of the histogenesis of mammary carcinoma evolved from the similar but much more extensive researches of Cheatle (Cheatle, G. L., and Cutler, M: Tumors of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment, London, J. B. Lippincott Company 1931), of Dawson (*Edinburgh M.J.* **40:** 57, 1933; **42:** 569 and 653, 1935) and Fraser (*Surg., Gynec. & Obst.* **45**:266, 1927). This concept recognizes that the epithelium of the breast is subject to some hyperplastic stimulus which may produce local or widespread benign neoplasia of various types. Papillary neoplasia, at first benign, may progress to carcinoma from one or multiple foci of origin, from duct rather than acinar epithelium. This process parallels the development of carcinoma from multiple polyposis of the colon or stomach. While this appears to be the most frequent mode of histogenesis, primary malignant transformation of duct epithelium directly, without passing through a benign papillary stage, is also possible and may account for the finding in a single case of a tiny area of intraductal cancer without the more usual picture of a distended cystic or papillary site of origin. This theory excludes squamous and transitional cell cancer, which are clearly related to the epithelium of the nipple.

DISCUSSION

IRVING GRAEF: This study was undertaken originally in an attempt to prepare a critique of the grading of mammary carcinoma. While severe criticism of the use of grading as a prognostic aid has been offered by some investigators—Dr. Plaut himself severely criticized the procedure in a general review—no statistical and careful serial study has been published to bring out the inefficacy of using random sections to determine the growth characteristics of a tumor. Soon it was learned in Dr. Koppelman's study that a great deal more may be said about the process when the whole gland is subjected to a simple macroscopic serial study, supplemented by the use of key blocks, which are simply those which represent the tumor and surrounding tissue.

CHICAGO PATHOLOGICAL SOCIETY

KATHARINE M. HOWELL, *President*

Regular Monthly Meeting, Jan. 9, 1939

EDWIN F. HIRSCH, *Secretary*

PATHOLOGIC AND ETIOLOGIC OBSERVATIONS ON AN INTESTINAL ENDEMIC OF NURSLINGS. ERNEST A. PRIBRAM.

An intestinal endemic among newborn infants observed in the fall of 1937 with extremely high morbidity and mortality was caused by Aerobacter mucosum

(Friedländer's bacterium). The micro-organisms isolated from the intestinal contents in life, as well as at necropsy, and from the lungs and heart at necropsy were highly virulent for mice. The virulence could be demonstrated by injecting, as well as by feeding, the cultures. The virulence was considerably lower and was eventually lost in strains transplanted daily and continuously on plain agar. There was a marked decrease of virulence in strains planted in the same way on dextrose and also on lactose mediums. There was, however, no loss but rather a gain of virulence in cultures grown constantly on galactose agar. Virulence was commensurate with slimy character and capsule formation. Mice fed cultures grown on plain agar or on dextrose or lactose agar gradually overcame the infection, whereas mice fed strains grown on galactose mediums had pure cultures of these bacteria in their stools; the bacteria replaced the normal intestinal flora and caused malnutrition of the infected animals. Lactose in diets of newborn infants may aggravate an intestinal infection with A. mucosum.

SEROUS HEPATITIS. HANS P. POPPER.

This is a report of investigations made in collaboration with Eppinger on serous inflammation. Capillaries are semipermeable tubes which retain the plasma proteins. The first manifestation of capillary damage is a loss of semipermeability with escape of proteins into the interstitial tissue. There the proteins, which are not reabsorbed by the blood capillaries and only gradually absorbed by the lymphatics, bind water and cause edema. This process, called serous inflammation, is known to occur in serous cavities and subcutaneous tissue. The significance of it in the soft interstitial tissue of the large parenchymatous organs has only recently been evaluated (Eppinger and Roessle).

Serous hepatitis is characterized by enlargement of the spaces between the liver cell cords and the blood capillaries, Disse's spaces. They become filled with protein granules, especially after fixation with a solution of glacial alcohol in absolute alcohol. In human livers serous hepatitis is often present, even after an agony of longer than usual duration, but it is especially marked in the livers of persons who died of infections, intoxications, coma or burns. In animals it can be produced by allylformiate, a representative of substances isolated from purulent exudates or spoiled meat. Serous hepatitis can be produced in many of the lower animals—for example, in the salamander. The development depends on the size of the reticulofibrous net in Disse's spaces. In man or dogs the space is large; in rabbits or guinea pigs it is small, and therefore in these animals the tendency to serous hepatitis is not marked. In acute intoxications of dogs, besides the changes of Disse's spaces, there is edema of the periportal fields and of the gallbladder bed, both having lymph vessels with an abundance of fluid. All three signs together form the triad of serous hepatitis.

To study the consequences of serous hepatitis, dogs were chronically intoxicated with allylformiate. After peroral or peritoneal introduction the effects were much severer than with subcutaneous injection. As quickly as twenty-four hours after administration of the drug there was complete destruction of the periphery of the lobules with rupture of the reticulofibrous framework. These ruptures, the severest degree of capillary damage, stimulated proliferations. Thus, finally a condition like cirrhosis developed in the course of two weeks. A cirrhosis very similar to that in man was produced in about six weeks by simultaneous use of small doses of allylformiate and bacteria intravenously. Then localized destruction of the periphery of the lobules appeared with formation of exudates and proliferation of the connective tissue. The rupture and occlusion of the communication between the bile capillaries and ducts explain the obstructive jaundice and, further, the proliferation of the smaller bile ducts, which is a result of stimulation by the rupture and attempts to reunite. In the human pathologic process the complete triad of serous hepatitis is not common. It is typically present in beriberi and in catarrhal jaundice, as far as one can judge from the clinical and postmortem observations in one case.

Serous hepatitis is, because of the specific structure of the liver, the first response of the organ to any irritation, irrespective of the cause. Further than this, it may disappear entirely or it may be followed by destruction of the parenchymatous cells or rupture of the framework built by the connective tissue (cirrhosis).

CARCINOMA OF THE PARATHYROID GLAND. KARL A. MEYER, PETER A. ROSI AND ALEX B. RAGINS.

Carcinoma of the parathyroid gland occurred in a Greek aged 56. The man had symptoms of hyperparathyroidism, such as pains in the bones and joints, a generalized fibrocystic disturbance of the bones, renal concretions, hypercalcemia, a decrease in the phosphorus of the serum and an increase in the phosphatase of the blood. Removal of the tumor ameliorated the pain in the bones and joints. Roentgenograms demonstrated definite recalcification of the fibrocystic tissues. The serum calcium and phosphorus and the blood phosphatase also reached normal levels temporarily. About one year after parathyroidectomy the pain returned, the serum calcium rose, the serum phosphorus fell and the serum phosphatase increased slightly. Roentgenograms disclosed increased fibrocystic changes of the bones. In the right side of the neck was a recurrent firm fixed mass. These late symptoms indicated persistent hyperparathyroidism.

RECOGNITION OF SUBGROUP A_2 AS A MEANS OF AVOIDING BLOOD TRANSFUSION REACTIONS. I. DAVIDSOHN.

Clinical experience, as it is expressed in the literature, suggests that the selection of a donor according to the known methods does not assure the absence of reaction to a blood transfusion, that such unexpected reactions are not uncommon when donors of the same blood group as the patients are employed, especially when donor and patient are of blood groups O and A, and that the reactions are particulary frequent when the so-called universal donors are employed.

Available serologic data suggest that subgroups A_1 and A_2, A_1B and A_2B may not be compatible, that the subgroups A_2 and A_2B are not infrequently mistaken for other blood groups, particularly for O and B, and that some reactions to blood transfusions, even fatal, are explained by the aforementioned circumstances. A high-titered, easily produced and highly specific immune rabbit serum enables a prompt recognition of blood group A, including the feebly agglutinating subgroup A_2. The proper dilution of the serum as determined by titration, makes possible a differentiation of subgroups A_2 from A_1 without delay. Both procedures may be completed within five minutes.

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KATHARINE M. HOWELL, *President*

Regular Monthly Meeting, Feb. 13, 1939

EDWIN F. HIRSCH, *Secretary*

IN VITRO AND IN VIVO ACTION OF CHRONIC INFLAMMATORY TISSUE ON CERTAIN ANTIGENS AND ANTIBODIES. KATHERINE E. HITE.

Bacteriologic and immunologic studies on chronic staphylococcic osteomyelitis demonstrated that some interaction occurs in the chronic lesion which markedly affects the immunologic aspects of this disease. The antihemolysin of the patient's serum, it was found, decreases during the chronic stages. In animals, the general effect of antigens and antibodies introduced into experimental fistulous tracts was significantly below that obtained when other routes of injection were used.

Typhoid vaccine introduced into the sinus tracts of patients failed to cause an increase in the agglutinin titer of the serum.

The present work has been concerned with the effect of pus and emulsions of fistulous tracts in rabbits on staphylococcus toxin, botulinus antitoxin and horse plasma in vitro, and the persistence of horse plasma in experimental sinus tracts. The presence of the test substance after the aforementioned treatment was determined as follows: staphylococcus toxin, by the hemolysin reaction with rabbit erythrocytes; botulinus antitoxin, by the mouse protection test against known toxin; horse plasma, by the reaction of anaphylaxis in sensitized guinea pigs. The results demonstrated that staphylococcus toxin, botulinus antitoxin and horse plasma were not destroyed by in vitro incubation for sixteen to twenty hours with pus and emulsions of sinus tracts and that sufficient horse plasma remained in sinus tracts for twenty-four and forty-eight hours to be detectable by anaphylaxis. These experiments tend to show that the effect of chronic inflammatory tissues in reducing the response of the host to antigens and antibodies contained within them is not essentially that of destruction of these substances but rather that the inflammatory tissue is an impermeable barrier to them.

EXPERIMENTAL CRYPTOCOCCIC INFECTION. L. R. KUHN.

Benham's contention that the Cryptococci causing meningitis and European blastomycosis cannot be readily differentiated was supported when a strain from a patient with only a subcutaneous lesion and bone involvement could not be distinguished from strains isolated from patients with meningitis.

The course of experimental cryptococcic infection in mice was studied. The infection may be detected easily by examining gram-stained preparations of tissues, particularly of the brain and lungs. Eight strains of Cryptococcus hominis could not be differentiated in their pathogenicity for mice. A ninth strain, however, consistently required more time to kill mice, and with this strain cysts in the brain frequently enlarged to such an extent that the parietal bones of the skull were elevated. The mice lived from one to three weeks after this became noticeable. This strain was morphologically, culturally and serologically like the others, and it appeared to multiply as rapidly in the mouse. Its pathogenicity and the pathogenicity of one of the other strains were not increased after fifteen consecutive passages in mice.

Unlike bacteria and other yeasts when injected into the peritoneal cavities of mice, each of 13 strains of cryptococci injected in quantities of 4,000,000 to 8,000,000 organisms in 0.1 cc. of 0.85 per cent solution of sodium chloride caused no greater exudation of neutrophilic leukocytes than did 0.1 cc. of saline solution. Heating, shaking with glass beads for one hour and the culture medium did not affect the in vivo chemotactic properties of the yeast for polymorphonuclear leukocytes. Cultures three to four weeks old attracted a few more of these cells; large numbers (25,000,000) of cryptococci attracted many more. Peritoneal exudates from 3 rabbits showed a similar deficient response to cryptococci.

SOME PHYSICAL AND CHEMICAL PROPERTIES OF STAPHYLOCOCCUS ENTEROTOXIN. ELLEN DAVISON.

Methods devised for the assay of staphylococcus enterotoxin are unsatisfactory. Biochemical properties and growth on differential mediums are not reliable criteria for the identification of enterotoxic strains. Oral administration and injection of the enterotoxin into monkeys and kittens have been the only methods yielding consistent results, but these methods are unsatisfactory for routine or quantitative assay. Other animals, the dog excepted, do not react. A better method of assay and an explanation for the peculiarities of this exotoxin may develop from studies of its physical and chemical properties.

Enterotoxin is antigenic. It is not destroyed by heat or formaldehyde. My studies of monkeys have demonstrated that the enterotoxic potency is diminished by heating. These animals were given intravenous injections of filtrates boiled for twenty, thirty or sixty minutes or autoclaved. Although the number of mon-

keys used for the 75 injections does not permit a definite conclusion, the trend is unmistakable. Attempts to purify the enterotoxin by precipitation with alcohol were unsuccessful. The enterotoxin was found resistant to alcohol that destroyed the staphylococcus lethal toxin. Chloroform and ether extracts of filtrates when fed to monkeys and injected into kittens had no effects. Enterotoxin was in the residue filtrate after the extraction. Enterotoxic filtrates were treated with ammonium sulfate at half and at complete saturation. None of the monkeys fed the material precipitated at half-saturation reacted, while 10 of 14 receiving that obtained by full saturation vomited.

EXPERIMENTAL STUDIES ON THE ADSORPTION OF BOTULINUM TOXIN BY KAOLIN-ALUMINUM HYDROXIDE IN THE INTESTINES OF ANIMALS. JAMES L. WATERS, G. M. DACK and L. R. DRAGSTEDT.

Guinea pigs were fed kaolin–aluminum hydroxide daily for seven days and on the eighth day were given fatal doses of botulinus toxin. In other experiments guinea pigs were fed toxin mixed with kaolin–aluminum hydroxide or were fed the supernatant fluid from such mixtures. Monkeys were fed toxin and kaolin–aluminum hydroxide mixtures and were given enemas consisting of the same mixture or untreated botulinus toxin. In vitro experiments to determine the effect of the gastric and pancreatic secretions of dogs on toxin adsorbed by kaolin–aluminum hydroxide were also performed.

Guinea pigs were not protected from botulinus toxin by the kaolin–aluminum hydroxide. Monkeys fed such mixtures survived. Only one monkey in the entire series had symptoms, and this one recovered. No symptoms appeared in monkeys which received toxin and kaolin–aluminum hydroxide enemas or untreated toxin enemas. There is evidence that the gastric secretions but not the pancreatic elute adsorbed toxin. The experiments also demonstrated that botulinus toxin is quantitatively adsorbed by kaolin–aluminum hydroxide.

DISCUSSION

G. M. DACK: The results indicate that there is no real basis for the use of kaolin-aluminum hydroxide in preventing the absorption of a toxic substance from the intestine.

NEW ENGLAND PATHOLOGICAL SOCIETY

CHARLES BRANCH, *President*

Regular Meeting, Jan. 19, 1939

GRANVILLE A. BENNETT, *Secretary*

PREINVASIVE CARCINOMA OF THE CERVIX. PAUL A. YOUNGE (by invitation).

At the Free Hospital for Women, Brookline, Mass., a group of 49 cases of preinvasive carcinoma of the cervix has been collected since Smith and Pemberton published their report of 16 cases (*Surg., Gynec. & Obst.* **59**: 1, 1934). In 5 of their 16 cases the diagnosis of carcinoma of the cervix was not made on the original biopsy slides until three and a half to twelve and a half years later, when the patients began to show invading carcinoma. In spite of the malignant outcome in these 5 cases, the consensus of most pathologists disagrees with the diagnosis of carcinoma on the original biopsy slides.

Since 1934, 2 more cases have been discovered in which invading carcinoma developed two and one-sixth and three and one-third years, respectively, after the original biopsies, in which the lesions were diagnosed as benign though now they are classified as preinvasive carcinoma.

Representative slides from both of these series have been shown to pathologists, who usually made the diagnosis of "chronic inflammation," "repair process" or "precancer." Because of the disagreement, one lesion was followed for one year without treatment. Three biopsies were made during the year, at the end of which time the lesion was 4 mm. in diameter and definitely invasive.

The morphologic character of the malignant, yet noninvasive epithelium is so characteristic and consistent that frequently a cursory low power microscopic inspection reveals its nature. It is the same type of epithelium as is sometimes found at the edge of an invading cancer of the cervix. At this point there is usually a sharp oblique line of demarcation, and the malignant epithelium extends along the surface for a short distance before it shows its invasive tendency. In preinvasive cancer the morphologic and cytologic picture is the same as is frequently seen in the marginal zone of a frank cancer, namely, incomplete differentiation, atypical cells and mitoses, variation in the size of the nuclei, large and often multiple nucleoli, occasionally multinucleated cells, hyperchromatic nuclei, and mitoses in the upper layers of the epithelium instead of in just the basal layer. The actual number of mitoses need not be increased over that of healing epithelium.

(Dr. Younge showed a representative group of photomicrographs in illustration of the 65 cases, including the case in which there had been no treatment, together with a few color photographs of the extirpated cervices demonstrating the gross pathologic appearance and results of the Schiller test. Several biopsy specimens from lesions which later were proved to be frank cancer, not included in this series, were shown to demonstrate the difficulties of making a correct diagnosis from one section. A group of slides showing the abnormal conditions, ranging from the most controversial to the more obviously malignant, were examined by several pathologists, and their diagnoses were tabulated and discussed.)

The conclusion from this study is that when biopsy of a specimen of the cervix shows preinvasive carcinoma, or carcinoma in situ, repeated biopsies will reveal either the same condition or actually invasive carcinoma.

DISCUSSION

SHIELDS WARREN: This is a most interesting and important presentation. Several years ago, when I first had the privilege of seeing some of these slides, I was much more conservative in my interpretation of them than I am at the present time. It is a serious question as to where pathologists should draw the line of actual malignancy. They used to think that without evidence of invasion there could be no malignancy. While it is difficult to give up this point of view, one must give very serious consideration to the conception of carcinoma in situ. Much as I have disliked the term, I feel that it probably is too useful to be discriminated against. Pathologists must be alert to recognize the changes so clearly pointed out by Dr. Younge and to follow them carefully in order to determine what happens to them.

Although a lesion such as was observed in these cases, showing atypical hyperplasia and numerous mitotic figures without invasion, must be considered malignant in the light of the experience presented, I believe that it should be more conservatively treated than a fully developed carcinoma. Pathologists certainly must urge biopsy of every suspicious lesion and have carcinoma of the cervix in mind from the onset of the child-bearing period. The comparatively youthful age of many patients with carcinoma of the cervix must be realized.

TRACY B. MALLORY: No one, I am convinced, can study the remarkable material which Dr. Younge has just presented and not be convinced both of the feasibility and of the importance of recognizing carcinoma in situ. It must be admitted that the gynecologists of the Free Hospital for Women have taught pathologists a most salutary lesson in their own field of histologic diagnosis. In retrospect it seems surprising that the pathologists in Boston should have been so slow in accepting the diagnosis of carcinoma in situ, since what was probably the first good histologic description of such a lesion was Dr. Bowen's description

of precancerous dermatitis, a lesion which has been known ever since as Bowen's disease. Perhaps, in fact, that has been part of the trouble. Pathologists had a mental image of carcinoma in situ derived from a study of cutaneous lesions and presumed that cervical lesions would present the same appearance.

A prophet is without honor in his own country. It seems only fair at this moment to point out that Dr. Frank Pemberton and Dr. George Van S. Smith began to talk about noninvasive cancer a full ten years ago. They sent slide after slide to various pathologists, who almost unanimously refused to make a diagnosis of malignant growth because there was no invasion. The end results which Dr. Younge has presented can leave no question as to who was right. It was not until Prof. Walter Schiller, of Vienna, came to Boston three years ago and lectured before this society on noninvasive cancer that the members granted to the foreign prophet the credence they refused to the local ones. Since that time, although conservative instincts still make them hesitate, I think that few of them have failed to diagnose carcinoma in situ on some occasion at least.

It must be admitted that the group at the Free Hospital for Women are exceptionally well fitted for such an investigation as this. The fact that the men who study the patients clinically also diagnose the conditions presented on the slides makes for a much closer correlation of clinical and pathologic observations than is possible in the average general hospital. Moreover, the final and most convincing stage of their demonstration, the repeated observation of a carcinoma in situ until it finally becomes invasive, is an unjustifiable experiment except in the hands of a clinician so sure of his control of the patient that he is confident the experiment can be interrupted before the patient's chances of cure have been jeopardized.

E. P. McCarthy: I have been interested in leukoplakia of the oral cavity, a lesion which runs somewhat parallel to lesions of the type presented by Dr. Younge.

Leukoplakia in the oral cavity rarely begins before the age of 40 and is often the result of a known chronic irritation. Such lesions often become verrucous. I should like to ask Dr. Younge whether or not lesions of the type he has described ever become verrucous, and what in his opinion is their cause.

George Van S. Smith (by invitation): We at the Free Hospital for Women have enjoyed not only giving our opinions concerning sections of the cervix that presented unusual and suspicious changes and then checking back to learn the clinical outcome but also studying previous biopsy specimens, whenever possible, from patients with obvious cervical cancer. I think it very likely that such minor procedures as trachelorrhaphy and cauterization may eliminate an occasional early cancer. For example, recently in reviewing sections prepared before 1910 we found two which appeared to us to contain malignant epithelium. Both were from specimens obtained at trachelorrhaphy. One of the patients died of carcinoma of the stomach (diagnosed at the Massachusetts General Hospital) over six years after trachelorrhaphy; the other died of alleged carcinoma of the endometrium over twenty years after trachelorrhaphy. Either these patients did not have preinvasive cancer or were cured by their plastic operations. Biopsy of a third patient's cervix in 1934 revealed what we considered one of these early malignant lesions—and our diagnosis was confirmed by a pathologist in Boston. It was decided to follow the patient carefully to determine future developments. At the time of the second biopsy, one month after the first, the cervix was thoroughly cauterized. I have been examining this patient periodically for four and one-half years—she is now well, with no evidence of cervical disease. Cauterization probably destroyed an incipient cancer. I think this answers Dr. Warren's question about "pulling our punches" on these early cancers, but we emphatically do not recommend these procedures as treatment for any cervix with indisputable cancer, no matter how early it is. Further, as Dr. Tracy Mallory emphasized, these procedures should not be relied on, even in patients with debatable lesions, unless they can be followed with certainty and examined often.

With the increase in biopsy material at the Free Hospital for Women and consequently the more frequent finding of these early malignant processes, we often have the disturbing thought that we must be missing some early cancers and that others must be missing a few. For example, last fall we treated a frank cancer of the cervix in a patient who had had a supravaginal hysterectomy for pelvic inflammation at our clinic three years previously, at which time the cervix was not considered sufficiently abnormal to "rate" biopsy or treatment. We probably missed a very early lesion in this patient.

PAUL A. YOUNGE: The treatment of preinvasive carcinoma of the cervix, or carcinoma in situ, should be exactly the same as for invading carcinoma, because frequently the first biopsy specimen shows only preinvasive carcinoma, whereas larger secondary specimens show definite invasion. This fact was emphasized during the presentation of the photomicrographs. If conservative treatment is desired, high amputation of the cervix may be done. If, however, careful pathologic examination of the extirpated cervix reveals invasion, radium and roentgen treatments should be given immediately, or as soon as the wound heals. Another method is complete hysterectomy, but, again, as with amputation of the cervix, if the lesion is found to be invasive, radium and roentgen treatments should be given.

I am glad Dr. Tracy Mallory brought out the fact that Dr. Frank Pemberton and Dr. George Van S. Smith began talking about this subject over ten years ago. Even before 1927 they began diagnosing these lesions as carcinoma, but general pathologists would not agree with them. However, in most cases they treated the patient for carcinoma in spite of the disagreement as to the diagnosis.

We do not associate kraurosis or verrucose-like lesions of the vulva with carcinoma of the cervix. Leukoplakia of the cervix has been reported a few times to develop into carcinoma, but this is open to question. Schiller does not believe that leukokeratoses develop into cancer. We have not followed any long enough to have an opinion. He also does not believe chronic inflammation is an etiologic factor. I feel that chronic inflammation may play a part in the development of carcinoma of the cervix, but the most important thing is to make routine biopsies of tissue from the junction of the normal squamous epithelium and the eversion, erosion or ectropion, as well as of all positive Schiller spots. Annual inspection of the cervix, with biopsy if indicated, in all women over 30 and in women of any age if they have borne children should be the established practice. This plus treatment of all eversions, erosions or ectropions will reduce the incidence and mortality of the disease.

GEORGE VAN S. SMITH: Dr. Younge's reply to Dr. McCarthy's question as to what may be a predisposing factor in the causation of cervical cancer demands, I believe, modification. In general, opinion is falling away from the idea that chronic inflammation may be etiologic. Knowing that the incidence of cancer of the cervix is greater in women who have been pregnant than in nulligravidas and that pregnancy is associated with a tremendous increase in estrogens and that these substances not only play a part in the induction of certain experimental cancers but also are closely related chemically to carcinogenic agents, I wonder whether these physiologic sterols may not act like, or even become, carcinogenic sterols in the patient susceptible to cancer.

Book Reviews

Parasitology, with Special Reference to Man and Domesticated Animals. Robert Hegner, Ph.D., Professor of Protozoology, Johns Hopkins University; Francis M. Root, Ph.D., Late Associate Professor of Medical Entomology, Johns Hopkins University; Donald L. Augustine, Sc.D., Assistant Professor of Helminthology, Harvard University, and Clay G. Huff, Sc.D., Associate Professor of Parasitology, University of Chicago. Cloth. Pp. 812, with 308 illustrations. Price, $7. New York: D. Appleton-Century Company, Inc., 1938.

This edition of the authors' well known textbook entitled "Animal Parasitology," follows the same plan as the original edition. The introduction, by Hegner, gives a survey of such general aspects of parasitism as animal habitats, the types of host-parasite relationship, the occurrence, origin, evolution and effects of parasitism and the rules of zoologic nomenclature. This is followed by considerations of the three natural divisions of parasitology: protozoolgy (Hegner), helminthology (Augustine) and present knowledge of those arthropods which are of parasitologic importance. The latter section was originally written by Root and has now been revised by Huff. In addition to these sections there is a bibliography covering 79 pages.

In general the conception and execution of the text are excellent. It stresses various fundamental biologic concepts in the field of parasitology and at the same time gives up-to-date information on various pertinent details of medicine, public health and technic. Criticisms regarding the completeness of various sections are largely matters of individual judgment, as no general textbook can aspire to completeness. Thus, it seems to this reviewer that certain aspects of important infections should have been considered in greater detail. The sections on the pathologic aspects of malaria and on immunity to this disease, for example, are very incomplete and contain misleading statements. Splenomegaly in malaria is ascribed "to distention with blood as a result of lowered vascular tone" without consideration of the additional factor of hyperplasia of various cellular elements after long-continued malarial stimulation. In the section on immunity the statement "Apparently the destruction of parasites within the host is due largely to the phagocytes, known as macrophages, that live on the walls of the blood vessels of the internal organs" is not very enlightening as to the origin of macrophages and will be interpreted by many as indicating a phagocytic nature of the common vascular endothelium of all internal organs. In spite of these minor shortcomings, the book will undoubtedly continue to hold its place as one of the outstanding texts on parasitology in English.

Cancer: Its Diagnosis and Treatment. Max Cutler, M.D., Associate in Surgery, Northwestern University Medical School, Chicago, and Franz Buschke, M.D., Assistant Roentgenologist, Chicago Tumor Institute, Chicago. Assisted by Simeon T. Cantril, M.D., Director, Tumor Institute, Swedish Hospital, Seattle. Cloth. Pp. 757, with 346 illustrations. Price $10. Philadelphia: W. B. Saunders Company, 1938.

The purpose of this book is to promote the application of the knowledge and methods at hand to the early diagnosis and treatment of cancer. Throughout the book the word "cancer" includes malignant tumors in general. The book opens with a comprehensive chapter on radiotherapy, in which are discussed such topics as the biologic effects of roentgen rays and of the gamma rays of radium, the methods of radiotherapy and the radiosensitivity of cancers. This chapter and the next two, on biopsy and on the spread of cancer, are of special interest to the

pathologist. The rest of the book is devoted to the systematic, orderly consideration of the diagnosis, the treatment and the results of treatment of cancer in all parts of the body except the eye and the central nervous system. There are 346 illustrations, all highly instructive. They show gross appearances of tumors in situ and otherwise, roentgenograms, anatomic relations of importance in the metastasis and in the treatment of cancers, appliances and methods used in radiotherapy, and the typical microscopic structure of important cancers. Minute details of morphologic appearance and histogenesis are left out of consideration purposely. Undoubtedly the lack of illustrations in the case of the thyroid, the urinary bladder, the testicle and the prostate will be supplied in future editions. The bibliography is consolidated conveniently at the end by chapters and alphabetically according to the names of the authors cited in the text. There is also a name index and a good, complete subject index. The book is an important addition to the literature on cancer in its clinical aspects. A particularly strong point is the presentation of the advances of radiotherapy of cancer. There is no recent book on clinical cancer in which the microscopic aspects of cancer are presented better on the basis of first hand knowledge. The pathologist will find here a thoroughly competent discussion of the structure and course of cancer in close correlation with the details of clinical diagnosis and treatment under different conditions.

Laboratory Manual of Hematologic Technic. Regena Cook Beck, M.A., M.D., Formerly Instructor in Pathology and Bacteriology at George Washington University Medical School; Head of the Department of Bacteriology, William and Mary College Extension; Pathologist to Stuart Circle Hospital and Director of the Stuart Circle Hospital School of Medical Technology, Richmond, Va. With a Foreword by Frank W. Konzelmann, M.D., Professor of Clinical Pathology, Temple University, Philadelphia. Cloth. Pp. 389, with 79 illustrations. Price $4. Philadelphia and London: W. B. Saunders Company, 1938.

This manual describes and explains in admirable fashion the various procedures of modern hematologic technic. Also, it interprets the results and their significance. There are five parts, dealing with the following topics: the methods of procuring blood specimens, the mechanism of clotting, the estimation of the hemoglobin content; the enumeration of blood cells and the determination of indexes; the cytology of blood; special studies used in hematologic practice; the special pathology of blood. The summaries, the lists of questions and the definitions of terms will be of great help to the student. The presentation is competent, comprehensive and clear. The book is well described in the following statement from the foreword by F. W. Konzelmann: "This manual is a valuable guide not only for the technologist, but all students of hematology will find it most helpful, whether they be pathologists, clinicians or medical students, for there is at the time of this writing no other single volume where so much information on the subject of procedure in hematology is contained between two covers." The book should have a place in every clinical laboratory.

Classic Descriptions of Disease with Biographical Sketches of the Authors. Ralph H. Major, M.D., Professor of Medicine, University of Kansas School of Medicine, Kansas City. Second edition. Cloth. Pp. 727, with 137 illustrations. Price $5.50. Springfield, Ill.: Charles C. Thomas, Publisher, 1939.

The first edition of this very interesting book was published in 1932. In the new edition sections have been added on malaria and yellow fever; also, additional readings and illustrations. Many of the biographic sketches have been rewritten, and the index has been revised. The book contains a great wealth of readings and information to illustrate the development of knowledge of disease.

Books Received

THIRTY-SIXTH ANNUAL REPORT 1937-1938 OF THE IMPERIAL CANCER RESEARCH FUND. Under the Direction of the Royal College of Physicians of London and the Royal College of Surgeons of England. Paper. Pp. 39. London: Royal College of Surgeons, 1938.

THE PASTEUR INSTITUTE OF SOUTHERN INDIA, COONOOR. The Annual Report of the Director for the Year ending 31st December 1937 Together with the Thirty-First Annual Report of the Central Committee of the Association for the Year Ending 31st March 1938. Paper. Pp. 89. Madras: The Madras Publishing House, Ltd., 1938.

MEDDELELSER FRA DR. F. G. GADES PATHOLOGISK-ANATOMISKE LABORATORIUM I BERGEN, 1938. Paper. Various pagination. 1939.

LA PONCTION STERNALE. PROCÉDÉ DE DIAGNOSTIC CYTOLOGIQUE. P. Émile Weil, Médicin des Hôpitaux de Paris, and Suzanne Perles, Chef de laboratoire a l'Hôpital Tenten. Paper. Pp. 184, with 25 illustrations. Price 75 francs. Paris: Masson & Cie, 1939.

WILLIAM P. WHERRY, BACTERIOLOGIST. Martin Fischer. Cloth. Pp. 293. Price $4. Springfield, Ill.: Charles C. Thomas, Publisher, 1938.

LEHRBUCH DER ALLGEMEINEN PATHOLOGIE UND DER PATHOLOGISCHEN ANATOMIE. H. Ribbert. Twelfth edition. Edited by Prof. Dr. H. Hamperl, Prosektor am pathologischen Institut der Universität, Berlin. Paper. Pp. 634, with 700 illustrations. Price 27 reichmarks. Berlin: F. C. W. Vogel, 1939.